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LIFE EXPECTANCY AND MORTALITY FROM SKIN AND LIP CANCER.*

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Sometimes a cured skin cancer patient develops another cancer to which he succumbs. Is the risk of such a discouraging metachronous combination of a surface and an internal cancer great?

According to Dublin and Lotka,[1] cancer shortens the life of the average person at 42 years by 5.2%, at 52 years by 6.2%, and at 62 by 6.8%. The shortening of life for the cancer victims themselves, is, of course, greater. The life shortening effect of cancer depends upon the site and the cellular type of the malignancy. Most of the surface cancers are relatively benign. However, as some of these patients die of the disease, this disease is bound to shorten the life even if it is not, or only very seldom, followed by an internal cancer.

In order to estimate the life shortening rôle of the skin and lip cancer one can depend less on the causes than on the frequency of death and on the time elapsed since the onset of the illness.

In this paper such an attempt has been made. I have studied 715 cases, from the histories of the lip and cheek epithelioma patients at the Kelly Hospital between 1921 and 1931 and the eyelid cases for the years 1921 to February, 1929. All cases were included, whether treated or not. Where the time of onset of the cancer was unknown, the age at the first entrance to the hospital was taken as onset. If a lesion had been persistent for a long time without signs of progress, the dates of previous surgical or Roentgen ray treatments were regarded as onset. In the case of metachronous epitheliomas, the first epithelioma was chosen as significant.

* This work was done while the author was a guest investigator in the Department of Biology of the School of Hygiene and Public Health of The Johns Hopkins University, using the records of the Kelly Hospital, Baltimore. For the results or conclusions reported the author is solely and entirely responsible.

Age Distribution. The average age of 695 patients with given age data at the onset of the disease was 58.6± 0.3 years. This is 11.1 years less than the average age at death from skin and lip cancer, as reported in the official statistics of the United States (69.7 years). In our material, the ratio of lip cancer (307 out of 715 cases) is much higher than in the official mortality statistics. The lip cancer patients were at the onset (2.5 years) as well as at the time of death (1.5 years) younger than the skin cancer cases. The real difference between the onset of the surface cancer and the death is, therefore, a little smaller than 11.1 years.

According to hospital records, patients suffering from internal or breast cancer are also much younger than one would expect on the basis of the mortality statistics. The reason for this is the selection of cases which undergo surgical treatment. However, such a selectional factor is not involved in the case of surface cancers admitted to a hospital known for its non-surgical methods.

TABLE 1.—AGE DISTRIBUTION OF FACE AND LIP CANCER PATIENTS OF BOTH SEXES.

Age.	Kelly Hospital, Baltimore.				U. S. Registration Area, 1930–1933.	
	Age at:				Age at death from cancer of:	
	Onset of disease.		Death.		Skin.	Lip.
	Absolute frequency.	Percentage frequency.	Absolute frequency.	Percentage frequency.	Percentage. frequency.	Percentage frequency.
29 . . .	9	1.3	..	..	1.8	0.6
30–39 . . .	51	7.4	1	0.6	2.3	2.4
40–49 . . .	105	15.1	6	3.6	5.5	6.6
50–59 . . .	180	25.9	26	15.5	11.3	14.1
60–69 . . .	192	27.6	41	24.4	19.3	24.8
70–79 . . .	130	18.7	58*	34.5	30.5	31.2
80+ . . .	28	4.0	36*	21.4	28.9	20.2
? . . .	20	..	1			
	715	100.0	169†	100.0	100.0	100.0

* Including 1 death after closed period of observation.
† Including 2 deaths after closed period of observation.

Generally, it is believed that persons suffering from skin or lip cancer are older than other cancer patients. This holds true for the age at death. Considering, however, that on the average the duration of surface cancer is much longer than that of an internal malignant tumor, one has to realize that at the onset of the illness there is practically no difference in age between sufferers from a skin or lip cancer and the total of all other carriers of a malignancy.

Mortality. During the first 5 years after the onset of the illness, there occurred 78 deaths; in the second quinquennium, 53 deaths; in the third, 29; and still later, 9 deaths. In order to evaluate these figures, they were related with the total number of years of the respective age group. Patients change in due time the age group to which they belong. Therefore, person-years instead of cases were counted and each one of the years which elapsed since the onset of the illness was placed in the respective age group.

Altogether the material collected covers 4860 person-years; 2603 of them belong to the first quinquennium after the onset of the epithelioma; 1462 to the second; and finally 795 person-years where the onset of the illness was at least 10 years earlier. The percentage of deaths rises with the number of years passed since the appearance of the tumor. In the first quinquennium, 3 deaths; in the second, 3.7; and in the further 5-year periods 4.9 deaths correspond with 100 person-years. By eliminating the different age distribution the differences in the death rates diminish, the standardized rates being 3.0, 3.3, and 3.8 respectively. The basis for these calculations is the age at the onset of the disease. In 295 of the 695 patients the onset was considerably beyond the time of the first attendance. Therefore, only 400 patients are an unselected unit. Among the 295 patients, however, there were some with a definite turn to the unfavorable course of the disease or even in a hopeless condition before their very first visit to the Kelly Hospital. The real death rates of an unselected material should therefore be lower, than indicated in our figures. On the other side, the 295 patients were at their first attendance at the Kelly Hospital survivors of other contingents of patients, with whom they shared an average of 3.2 years. Probably, during these 3.2 years of the cohort to which they belonged formerly a number of patients died. Applying the general mortality rates to these 295 patients one may assume that they should be complemented by 31 deaths, 24 of which should have occurred during the first quinquennium of the disease. Thus the standardized death rate of the first 5-year-period will increase to 3.9, of the second to 3.5 and of the later periods to 4.2%.

The number of actual deaths differs from that expected according to the U. S. Life Tables which were used in this paper as a basis for all calculations.

TABLE 2.—DEATH RATES PER 100 PERSON-YEARS IN FIRST AND ALL SUCCEEDING 5-YEAR-PERIODS AFTER ONSET OF DISEASE, KELLY HOSPITAL. PERSONS WITH FACE AND/OR LIP CANCER.

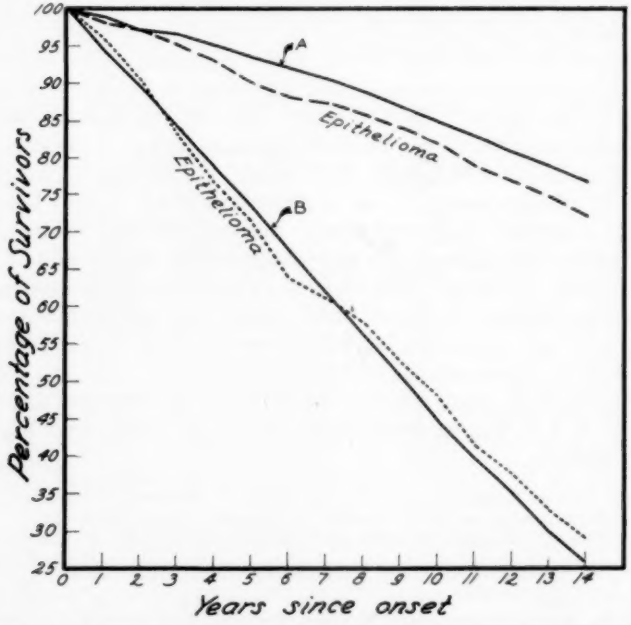
Age at time of observation.	First quinquennium.			All following quinquennia.			Death-rate for all years.	U. S. Life Table, 1929–1931; death-rate, 100qx.*
	Person-years.	Deaths.	Death-rate.	Person-years.	Deaths.	Death-rate.		
39 . .	174	1	0.6	43	..	..	0.46	0.43
40–49 . .	409	3	0.7	268	3	1.1	0.89	0.81
50–54 . .	304	5	1.7	240	6	2.5	2.10	1.30
55–59 . .	377	10	2.7	279	5	1.8	2.30	1.90
60–64 . .	371	8	2.2	362	9	2.5	2.30	2.75
65–69 . .	360	13	3.6	353	11	3.1	3.40	4.10
70–74 . .	286	12	4.2	323	17	5.2	4.80	6.25
75–79 . .	169	10	5.9	225	19†	8.4	7.40	9.40
80– . .	122	15	12.3	134	21†	15.7	14.00	16.00
? . .	31	1	3.2	28	..	..	1.70	
	2603	78	3.0	2257	91‡	4.1	3.50	3.90

* The symbol 100qx denotes the chance for 100 persons, at the age x, of dying within 1 year, namely between the ages x and (x + 1).
† Including 1 death after closed period of observation.
‡ Including 2 deaths after closed period of observation.

In the ages below 60 there are more, and in the higher age groups fewer deaths than would be expected from the general life-table.

Of all patients with given age 168 died, whereas 191.8 deaths would be expected (30.8 deaths before, and 158.7 after the first attendance at the Kelly Hospital). In the age groups below 60 years, 33 deaths were registered and only 26 (=7 + 19) calculated, the respective figures for the higher ages being 135 and 163.5 (=23.8 + 139.7).

Assuming, in conformity with Welch and Nathanson,[2] that the mortality of cases lost is about as that of the group which remained under care, I calculated mortality and survival rates for each successive year after the onset of the disease. From the fourth year on, patients at the age of 21 to 59 have lower survival rates than the average (curve *A*), whereas persons with onset of the epithelioma at the age above 59, after 7 years of the illness have passed, show higher survival rates than the general population (curve *B*).



GRAPH 1.—CURVE OF SURVIVORS OF 726 PATIENTS SUFFERING FROM SKIN OR LIP EPITHELIOMA.

Expectation of Life. If the 695 skin and lip cancer patients were a random sample of the general population, then they should expect to live, according to their age distribution at the onset of their illness, another 11,626 years. (By using life tables for the Maryland population, the life expectation would have been smaller than here.) That makes an average of 16.7 years per person. Of the 11,626 years only 4800, *i. e.*, 40% were covered by observation, counting the time from the onset of the illness up to the death (one group), or up to the time of our investigation (second group), or up to the date

of disappearance (third group of patients), respectively. The younger the patients, the smaller the part of the life expectation which could be tested by observation.

TABLE 3.—EXPECTATION OF LIFE AT ONSET OF THE FACE AND LIP EPITHELIOMA AND THE NUMBER OF YEARS TESTED SINCE THEN. (KELLY HOSPITAL.)

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Age at onset.	No. of patients.	Expected years $\mathring{e}_x$*		Patients who							Years which remain to be covered.
				Died.			Did not die.				
				Lived since onset.						All.	
		Total.	Av.	No.	Yrs.	Av.	No.	Yrs.	Av.	Yrs.	
21–39	60	2045	34.1	6	50	8.3	54	442	8.1	492	1553
40–49	105	2690	25.6	16	142	8.8	89	843	9.5	985	1705
50–59	180	3353	18.7	31	189	6.4	149	1206	8.1	1404	1949
60–69	192	2400	12.5	58	396	6.8	134	837	6.2	1233	1167
70–74	77	677	8.8	24†	120	5.0	53	243	4.6	363	314
75+	81	462	5.7	33†	157	4.8	48	166	3.5	323	139
	695	11,626	16.7	168	1063	6.3	527	3737	7.1	4800	6825

* $\mathring{e}_x$ is the symbol for the expectation of life at the age x, called also mean after-life-time at that age. Calculation made on basis of U. S. Life Table, 1929–1931.

† Including 1 who died a few months after closed period of observation.

In order to fulfill the normal life expectancy of the 695 patients the 527 persons still living at the end of the observation period (Column 8, Table 3) would have to live another 6825 years (Column 12). A random sample of 527 individuals of the given age distribution has a life expectancy of 7135 years. However, among these 527 cases there were 14 with recurrent epithelioma (according to the age: 3+1+5+3+1+1) and 46 with uncured glandular metastases or already in a hopeless condition or persons with a primary cancer of an internal organ (8+7+7+12+9+3). For the sake of argument, I abandoned entirely these 60 cases, counting them all *a fond perdu*, as if they all had died on the first day after the end of the observation period. At this day the normal $\mathring{e}_x$ of the 60 cases would have been 1043 years, thus leaving for the remaining 468 cases an $\mathring{e}_x$ of 7135–1043 = 6092 years. Considering that 6825 years had to be covered, a deficit of 734 years remains. That is about 6% of the total number of years the 695 patients (Table 3, Column 2), had had to live at the onset of the disease.

Depending on the age, the deficit is larger or smaller. Of the persons who developed an epithelioma at the age of 20 to 49 years, at the end of our observation 115 were free of symptoms and other 9 persons still ill but without any complications (as metastases, recurrent epitheliomas or primary internal tumors). The $\mathring{e}_x$ of these 124 persons at that time was 2666 years, whereas 3258 still had to be covered. Thus the 165 persons with an onset of the illness between 20 and 49 years of age will probably have a final deficit of $\frac{592 \times 100}{4735} = 12.5\%$ of their life expectancy as indicated in Column 3 of the last table. The higher the age at which the epithelioma

first appeared, the lower this final deficit. Cases with onset of the disease at 50 to 59 probably will fall short only 4.0% of the normal life expectancy, and in those of the age group 60 to 69 the final deficit will apparently not exceed 3.2%. Patients who developed their first epithelioma at an age above 70 seem to live at least as long and probably longer than the average of persons of the same age. Excluding from the 101 persons still alive (Column 8, ages above 70) those with a recurrent epithelioma or with metastatic affections and with an internal cancer, we got 73 persons free of symptoms and 15 still uncured but without any complications. The further life expectancy of these 88 persons was 438 + 92 = 530, whereas only 453 years (Column 12) had to be covered. It is a surplus of $\frac{77 \times 100}{1139}$ = 6.8%.

Life Expectancy of Cases Which Were at Least 6 Months Under Observation. A considerable number of the patients recorded in the former tables were only for a very short time under observation. The endeavors of the Kelly Hospital to follow them up were fruitless. By omitting all who were lost after less than half a year, except those who died during this time, the total number of cases (of known age) shrinks to 547. On the average the fatal cases lived 6.3 years, and the non-fatal cases 9.3 years from the onset of the disease (Columns 5 and 8, Table 4). Of the total life expectancy (Column 3) 4577 years, *i. e.*, 48.6% are covered by observation. This percentage depends on the age of the patient, rising from 36 in the youngest age group to 75% in the age group above 70 years.

Excluding from all further calculations 39 persons suffering from a recurrent* or metastatic epithelioma or from an internal malignancy,† there remain 340 persons (317 free of symptoms, and 23 still ill) with a further life expectancy (according to the U. S. Life Tables) of 4324 years, while 490 more would be necessary in order to cover the total $\mathring{e}_x$ of the 547 cases at the onset. The final deficit is, thus, 5.2%.

In general, Table 4 confirms the former results. Patients suffering from an epithelioma at ages below 49 have a larger deficit (about 10%) than those whose first epithelioma develops at 50 to 69 years of age (4 and 3% respectively); whereas patients with onset above 70 most probably will live longer than the average population. Of the 57 persons still alive at the end of our observation period, 47 were free of symptoms and 3 still ill but without any complications. These 50 persons had a further life expectancy of 271 + 17 = 288 years while only 204 years remained to be covered. Neglecting entirely the further life of the complicated cases we realize for the entire group of patients over 70 a life surplus of probable $\frac{84 \times 100}{815}$ = 10.3%. One will, of course, remember that 208 of the 547

* 3 + 4 + 2 + 2 = 11 cases.

† 9 + 5 + 9 + 5 = 28 cases.

patients do not show any mortality during the 731 years of illness in the pre-Kelly Hospital period, while according to the Life Tables 23.2 persons would have to succumb to one of the many causes of death, either cancer or not. Of the 23.2 persons, 10.4 were to be placed in the age group above 70, and added to the 114 patients (Column 2, Table 4). This, however, does not turn the positive life balance of the group into a negative one.

TABLE 4.—LIFE BALANCE OF PATIENTS WHO EITHER DIED OR WERE AT LEAST FOR SIX MONTHS UNDER CARE AT THE KELLY HOSPITAL.

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
			Patients who							
Age at onset of disease.	No. of cases.	Expected years of life, $\mathring{e}_{x.}$*	Died.		Did not die.			All.	Years which remain to be covered.	
					Lived since onset.					
			Persons.	Years. av.	Persons.	Years.	Av.	Years.	Total.	% of expectation.
20–49	139	3980	22	8.7	117	1233	10.5	1425	2555	64.1
50–59	148	2772	31	6.4	117	1162	9.9	1360	1412	51.8
60–69	146	1824	58	6.8	88	781	8.9	1181	643	34.9
70+	114	815	57	4.9	57	334	5.9	611	204	25.0
	547	9390	168	6.3	379	3510	9.3	4577	4814	51.4

* See footnote to Table 3.

The Mortality of Persons Successfully Followed Up. Up to the death or the time of inquiry, 427 persons of known age were traced. Their pre-Kelly Hospital period of illness covered an average of 1.1 years per case.* After they attended the hospital, the 261 persons still alive lived 2736 years (an average of 10.5 years each), whereas the 168 fatal cases lived 851 years (an average of 5.1 years each). Taking only the time after the Kelly Hospital had been attended, there would be expected for the 20 to 59 year-old patients 19.6 deaths and for the higher age groups 138.1. There occurred, however, 33 and 135 deaths.

TABLE 5.—FACE AND LIP CANCER PATIENTS FOLLOWED UP SUCCESSFULLY. MORTALITY AT THE TIME AFTER THE FIRST ATTENDANCE TO THE KELLY HOSPITAL.

1.	2.	3.	4.	5.	6.
				Number of deaths.	
Age.	Persons at the age of attendance.	Years observed at the age.	Life table, $100q_{x.}$*	Expected.	Actual.
				At the age of Column 1.	
20–39	30	104	0.43	0.46	1
40–49	62	436	0.89	3.90	6
50–59	118	898	1.73	15.20	26
60–69	121	1132	3.58	40.25	41
70–79	74	786	7.51	59.00	58†
80+	22	223	17.30	38.60	36†
	427	3586		157.60	168‡

* See footnote to Table 2.
† Including 1 death after closed period of observation.
‡ Including 2 deaths after closed period of observation.

Life Duration of the Prospective Skin and Lip Cancer Patients. At any chosen age any population may be divided into *a*, persons

* Living cases 1 and dead cases 1.2 years; patients who could not be traced had a pre-Kelly Hospital period of 1.7 years on the average.

already suffering from cancer; *b*, persons who in the future will develop a surface cancer; *c*, persons who in the future will develop an internal malignancy; and, *d*, individuals who never will produce a cancer. Let us now consider the situation at the age of 40 for persons who in the future will develop a surface cancer. Have they a shorter life expectancy ($\mathring{e}_{40}$) than an average person at that age?

The answer is: no. On the contrary, they have a higher mean after-life-time than the average population. Persons who later on develop a skin or lip cancer have, of course, by definition a long precancerous period without any deaths. This period lasts from 40 to 60.8 years of age (according to the material of the Kelly Hospital). In the general population of all who lived at 40 years, 24% die during these 21 years. The question to be answered is, therefore, whether the gain of life in the precancerous period is counterbalanced by the excess mortality after the onset of the surface cancer. The answer is again: no. Of all patients above 40 years of age, the life had been checked for 6.9 years on the average. During this time 29%* of the patients died, whereas on the basis of the life table only 21% is expected. The excess mortality eliminated thus a great part of those who were "supernumerary" at the beginning of the cancer period. After the closed period of observation 71% of all patients were still alive and, on the average, 67.7 years old. The total normal $\mathring{e}_{40}$ being 29.7 years, the persons still living would have to live another $\frac{2 \times 100}{71} = 2.8$ years in order to fulfill the total mean after-life-time. During this time 12% would normally die, and further $\frac{16 \times 100}{71} = 22.5\%$ would have to die in order to counterbalance the gain of life in the precancerous period (40 to 60.8 years of age). That is improbable.

On account of the death-free period by definition, it may be argued that a comparison of the life expectancy of *future* epithelioma patients at the age of 40 (or 50, 60, and so on) with the average population is methodologically dubious. However, no objection can be made to a comparison between persons who in the *future* will suffer either from a surface epithelioma or from an internal cancer. The death-free precancerous period is common to them and about of the same length. Different in this case is the duration of life after the onset of the disease.

In the United States during 1935 men at ages above 40 who died from causes other than cancer were on the average 70.5 years old. The corresponding figures for men who died of cancer of skin or lip were 70.9, and for all men who died of an internal cancer 65.4 years only. In spite of the gain in life during the precancerous period,

* Here are also included the probable deaths calculated for the pre-Kelly Hospital period.

the victims of an internal malignancy lost 5.1 years of life, whereas the victims of a surface cancer continued to live after having fulfilled the average life expectation. As a large part of skin and lip cancer patients do not succumb to cancer, the real difference in the age at death between those who developed a skin or lip cancer and the other two groups of the population is greater than 0.4 and 5.5 years respectively. Including women into calculation the differences in favor of the carriers of a surface malignancy become conspicuously larger, the mean age at death for all over 40 being 63.3 (internal cancer), 69.4 (causes other than cancer), and 71.8 years (victims of skin and lip cancer).

Discussion. Possibly the material analyzed in this paper is not a fair representation of the average surface cancer patients in the population. A representative material, such as that of the Radium Hemmet in Stockholm, shows more persons freed of symptoms (70% of all skin and 62% of all lip cancer cases; 59% in all of our surface cancer cases), less cancer deaths and death candidates (5%, against 8 in our material) and it shows also a little higher percentage of noncancerous deaths (17%, against 14.5% in our study). In the material of the Kelly Hospital advanced and complicated cases are apparently more frequent, especially in the younger age groups. Still less favorable are the figures for lip cancer reported by Welch and Nathanson.[2*]

According to the reports obtained, among the 715 patients of the Kelly Hospital there are 12 who after the epithelioma developed an internal primary tumor. One cannot rely upon these diagnoses. Some of these tumors were rather metastatic, some more likely synchronous. Only a small part of them died in a hospital. In 5 of these cases death occurred at over 70 years. The youngest victim died at the age of 51; the cause of death was a cancer of the stomach and the patient died 2 years after the surface epithelioma appeared. It was, therefore, rather a case of synchronous than of metachronous multiplicity of tumors. In any case, as far as these data indicate, in our study the high mortality of patients at 20 to 59 is not due to a high incidence of second primary tumors in inner organs; it is rather due to a selection of complicated cases.

Summary and Conclusions. At the onset of the disease, carriers of an epithelioma of skin or lip are about as old as the average of all other cancer patients. At the time of death cases of skin and lip cancer are older.

The influence upon the life expectation and mortality depends on the age at onset. Skin and lip cancer cases below 60 years have in our material an increased mortality and a shortened life expectancy, as compared with the average population at the same age.

* Their material was collected in the Pondville and Huntington Hospital, Massachusetts. Only epidermoid and adenocarcinoma cases were considered, the basal cell cancer cases omitted.

Cases with onset of the epithelioma at ages above 70 have a lower mortality and a higher life expectancy.

At the beginning of the "cancer age," at 40 the total group of future carriers of a surface cancer have most probably a future life surplus, compared with the total population of the same age. This indicates that the primary internal cancers developing in those who already have or have had surface cancer are not frequent enough to diminish the life expectancy in this group or to frustrate the value of therapy of the surface malignancies.

REFERENCES.

(1.) **Dublin, L. I.**, and **Lotka, A. J.**: Length of Life: A Study of the Life Table, New York, The Ronald Press Company, 1936. (2.) **Welch, C. E.**, and **Nathanson, I. T.**: Am. J. Cancer, **31**, 238, 1937.

SCLEREDEMA ADULTORUM.

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The syndrome which Buschke[1] described at the beginning of the century under the designation "scleredema adultorum" has been accorded scant attention in the American literature. Particularly since the report by Epstein[4] 7 years ago, dermatologists have been alert to recognize the characteristics of scleredema, but internists apparently have not been adequately aware of this distinctive although rare disease. Unfamiliarity has at times promoted confusion of scleredema with the grossly similar entity, scleroderma—an error which carries with it serious prognostic implications. There have been cases in which scleredema not infrequently has been mistakenly diagnosed as acute edematous scleroderma, and the subsequent favorable course has led to unwarranted conclusions regarding the benign nature of certain instances of "scleroderma." Because the onset of scleredema is associated generally with an acute infection, because the outlook for recovery of the patient is excellent, and because the internist is usually the first and sometimes the only medical attendant in such a case, we believe that a general account of this disease might be of interest to physicians other than dermatologists. The pertinent literature has been reviewed in recent contributions by Touraine, Golé and Soulignac,[19] and Sweitzer and Laymon.[18] In this paper we shall present a compilation of the clinical and pathologic features of scleredema as the disease has been observed by us at The Mayo Clinic.

Material. The material reported on herein represents a group of 15 patients of whom 10 were female and 5 were male. The predilection of the disease for the female sex is also borne out in the literature. Ages ranged from 2 to 53 years. Most of the patients (12) were less than 30 years old, and the largest single age group was the third decade, in which decade alone were 8 patients. Neither occupation nor social factors played an apparent rôle. Study of the seasonal incidence in our series showed a remarkable restriction of the onset of the disease to the months between late fall and late spring.

Symptomatology. In all but 3 of the cases initial symptoms were preceded by an acute infectious disease, the nature of which in each case is indicated in Table 1. Predominance of infections of the respiratory tract (influenza, tonsillitis, scarlet fever) is conspicuous. The interval between invasion by the antecedent disease and the first appearance of edema varied from a few days to 6 weeks. During this period of "incubation" or latency 2 patients complained of general weakness and malaise, and 2 others experienced mild articular pains. In most of the cases, however, the interval was essentially asymptomatic, the patient having been regarded as normally convalescent or entirely recovered from the recent infection when the cutaneous signs characteristic of scleredema presented themselves. So far as could be determined, the onset of scleredema was at no time accompanied by fever.

Swelling started on the necks (often initially regarded as "stiff neck") of 12 patients, on the faces of 2, and over the abdomen of 1. Usually, the involvement spread rapidly to occupy extensive portions of the body, in 6 cases becoming generalized. In the other cases the disease was confined to the upper portions of the body, extending down to the abdomen or buttocks and including, in 2 instances, the thighs. Even in cases of generalized distribution, the lower extremities were often involved but slightly. Edema conspicuously spared the feet in every case, and the hands in every case save 1. As a rule the evolution was rapid, requiring less than 1 week or 2 for completion, but in 2 cases the edema spread more slowly, over a period of 2 to 3 months. When the patients were seen at the clinic, the disease in all cases had already attained its definitive extent.

The affected skin subjectively was described as stiff or rigid and restraining. Movements of affected parts were thereby materially restricted. Pain was notably absent, and in only 2 instances were paresthesias experienced. The degree of stiffness and edema was observed by 2 patients to fluctuate from day to day, and in 1 instance the patient noticed exaggerated tightness during the week preceding the menses. Occasionally, a patient reported dyspnea on exertion, caused by constriction about the neck or thorax, and in a few instances symptoms of slight dysphagia or hoarseness were present.

One patient experienced weakness and tenderness of the muscula-

ture of the extremities and shoulder girdle. Although biopsy was not performed, it was considered likely that muscular involvement by the disease had supervened.

The appearance of the skin was sometimes deceptive, in that few abnormalities were visible on casual inspection. The surface usually revealed no sheen or prominence of follicles. The minute markings were generally preserved, except in a few cases which displayed a smooth, glossy, pseudo-atrophic appearance. The color was at times pale, although the pallor was not striking, and the glazed ivory or alabaster hue of scleroderma was entirely lacking. One patient exhibited diffuse light brownish discoloration over the affected portions, and another presented discrete plaques of hyperpigmentation over the extremities. In most cases the face appeared somewhat puffy, and the deeper folds were diminished or obliterated, bestowing a "masked" appearance on the patient. The eyelids were usually not swollen. In 2 cases the tongue was involved, with consequent restriction of movement.

On palpation, an unanticipated degree of change was usually elicited. The skin provided a sensation of thickness, of deep, resistant, lardaceous or brawny induration, and it could not be picked up in large folds or moved freely over subjacent tissues (Figs. 1 and 2). Instead, it appeared usually to be fused with or bound inflexibly to the subcutis, as if it were either congealed or in a state which has been appropriately compared to the state produced by homogeneous infiltration of the deeper layers with paraffin.[16] No pitting resulted from firm pressure. The borders of involvement were not distinct; merging took place gradually with the normal skin.

Two patients had mild cyanosis of the otherwise unaffected fingers and toes, and they complained of numbness and tingling in the distal parts of the extremities. Another patient showed cyanosis of the fingers only. Although these phenomena might reflect a vasomotor abnormality, the possibility was considered also of superficial venous engorgement induced by the constricting, proximally situated infiltrate. Increased sweating of hands and feet was complained of by these 2 patients, and 1 additional patient exhibited generalized excessive sweating.

The duration of the disease in the case of patients we have been able to follow ranged between 3 months and 3 years. So far as could be ascertained, involution was complete wherever "cleared" or "healed" is indicated in Table 1. Recurrences after healing are not, however, uncommon. Two of our patients furnished such a history, the interval between attacks lasting 2 years in 1 instance, and 20 years in the other.

Laboratory data yielded little of diagnostic significance in our material. Morphologic and chemical constituents of the blood showed no important anomalies. Determinations of the basal

metabolic rate were normal in the 7 instances in which they were performed. The patient suspected of having muscular infiltration by scleredema excreted increased quantities (up to 400 mg.) of creatine as demonstrated by 24-hour specimens of urine.

TABLE 1.—SCLEREDEMA ADULTORUM: SUMMARY OF 15 CASES.

Case.	Age, sex.	Antecedent disease.	"Incubation" interval.	Site of onset.	Development and duration.	Miscellaneous.
1	27 F	Spontaneous abortion	5 weeks	Neck	Spread over chest and arms; nearly clear in 8 mos; slight stiffness of neck remaining	Later pregnancy did not impede involution.
2	37 F	"Rheumatism"	...	Neck	Spread to face, upper trunk and arms; greatly improved in 2 mos.	Recurrence 20 yrs. later, lasted 1 yr.
3	18 M	Influenza, mastoiditis (right)	6 weeks	Right cheek	Generalized in 10 days; healed in 9 mos.	
4	25 M	Influenza, arthritis left knee	1 month	Neck	Extended over head, trunk and upper extremities in 5 days; cleared in 6 mos.	Biopsy.
5	53 F	Infected thyroidectomy incision	6 weeks	Neck, in zone of infection	Generalized; extremities mildly involved. Improved rapidly first 4 mos.; healed within 2 yrs.	Hyperpigmentation. Biopsy.
6	2 M	Scarlet fever, otitis media, mastoiditis	5 weeks	Head, neck, tongue	Rapidly generalized; marked improvement first month; cleared in 8 mos.	
7	39 M	Influenza	2 weeks	Abdomen	Slowly spread to neck, face, tongue, arms, trunk and thighs; healed in 3 mos.	Slight dysphagia and hoarseness. Pigmented plaques over extremities.
8	6 F	None?	...	Neck	Rapidly generalized; recovered in 1 yr.	Biopsy.
9	20 F	None	...	Neck, elbows	Slowly generalized; cleared in 3 yrs.	Slight dyspnea and hoarseness. Cyanosis, hyperhidrosis and numbness, hands and feet. Biopsy; recurred 1 yr. later; rapid involution.
10	25 F	Tonsillitis, cervical lymphadenitis	1 month	Neck	Spread to face, trunk, upper extremities and thighs. Moderately improved 1 yr. later	Numbness, cyanosis, hyperhidrosis, hands and feet. Biopsy.
11	6 M	Measles	2 weeks	Face	Slowly generalized. Healed in 3 mos.	
12	20 F	None	...	Neck	Spread to face, upper extremities and chest in several days	Fingers cyanotic.
13	27 F	Influenza	1 month	Neck	Extended slowly over shoulders and chest. Healed in 8 mos.	
14	26 F	Tonsillitis, otitis media	2 weeks	Neck, cheeks	Spread to face, trunk, upper extremities (including hands). Stationary after 4 mos. Improved in 7 mos.	Pregnant (7 mos.) at onset; increased stiffness postpartum. Slight dysphagia; hyperhidrosis.
15	29 F	Scarlet fever	1 month	Neck	Spread to face, scalp, trunk and arms. No improvement after after 2½ yrs.	Muscular tenderness and weakness, dyspnea, creatinuria.

Pathologic Considerations. Specimens of skin were excised for microscopic examination from 5 patients. Study of the sections

prepared by routine histologic methods revealed few striking abnormalities. The epidermal outline exhibited the usual undulatory pattern, indicative of the delicate wrinkling which usually persists over the cutaneous surface. The epidermis itself presented no significant changes aside from hyperkeratosis and follicular plugging in several sections. In the cutis the chief findings were disclosed in the middle and deep portions, where the collagen bundles were somewhat swollen here and there, often staining homogeneously and separated by clear spaces (Fig. 3). Alterations in connective tissue were not, however, especially outstanding; 2 specimens, indeed, showed no deviation from the normal. In only 1 instance was the pars papillaris moderately homogenized. A distinct perivascular infiltrate occurred at times, the cells consisting mostly of lymphocytes and fibroblasts. In 1 case mild swelling was observed in a few of the vascular walls, and in another a number of vessels occupying the lower cutis and subcutis were dilated. There was no morphologic disturbance of the lymphatic vessels. Cutaneous appendages appeared also to be intact, although in one section hair follicles and sebaceous glands were atrophic. The elastic tissue in general revealed no peculiarities; nor were changes demonstrable in the cutaneous nerves or in the subcutaneous fatty tissue. Biopsies of muscular tissue, obtained from 2 patients, showed a normal structure.

Freund,[6] in 1930, was able by special fixation and staining to demonstrate in the interstitial edematous spaces a net of metachromatic "mucin-like" substance which he believed was, like mucin, a glycoprotein. In our formalin and alcohol-fixed tissue, this metachromatic tinctorial reaction could not be produced. The substance contributing to the edema is not in a fluid state, because incision of the skin does not cause its exudation.

Differential Diagnosis. The most important single problem of diagnosis is encountered in early diffuse scleroderma. In the literature scleroderma and scleredema have been repeatedly confused, as the paper by Touraine and his associates testifies with abundant documentation. In the primary, edematous stage of diffuse scleroderma, differentiation from scleredema may at first be difficult or impossible,[12] for the skin at such a stage exhibits a firm swelling similar to that caused by scleredema, and which also may follow in the wake of a previous infection. Nor may the histopathologic changes of scleroderma be sufficiently distinctive at this time to be of aid.

Prodromal articular and vasomotor symptoms often usher in diffuse scleroderma.[13] Earliest signs consist in gradual diminution of the normal folds, waxy or glossy sheen of the skin, and a loss of facial expression; sclerodactylia, also, may appear shortly. The color assumes an ivory tint. Induration, however, does not spare the superficial portion of the skin, as it usually does in scleredema.

FIG. 1.—(Case 4.) Scleredema adultorum of 5 weeks' duration, showing increased consistency of the skin which resists manipulation.

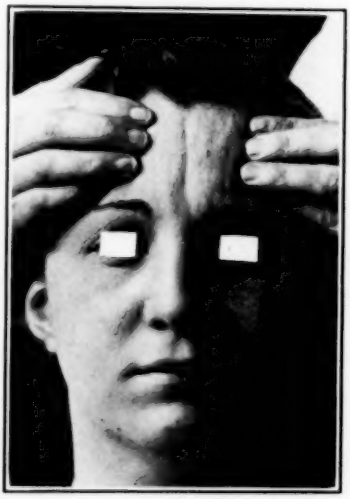

FIG. 2.—(Case 9.) Scleredema adultorum which had been present for 8 months. The superficial wrinkling produced by attempts to pick up the skin indicates the characteristic deep induration of this disease.

FIG. 3.—Skin from abdomen of a patient (Case 9), showing perivascular infiltrate in the upper cutis, homogenization of collagen, and edematous spaces between collagen bundles (hematoxylin and eosin. × 60).

Later, the characteristic picture of hidebinding and atrophy is seen, with rigid, shrunken, mask-like facies, limitation in movements of the mouth and tongue, wasting of subcutaneous tissue and muscles, restricted mobility of joints, and bronzing of the skin. This relentless, progressive, atrophic development does not occur in scleredema. The essential histopathologic changes consist of vascular thickening with obstruction of the lumens, perivascular cellular infiltration, and hypertrophy and sclerotic homogenization of collagen.

Dermatomyositis[14] early in its course likewise may at times imitate scleredema closely. One of us (O'Leary[12]) has called attention to this possibility on several occasions. The fact that the pathologic process in scleredema sometimes invades the musculature can render its resemblance to dermatomyositis all the stronger. Indeed, it may be necessary in certain cases to reserve judgment until the course of the disease has been observed over a reasonable length of time, because even biopsy may give indefinite results. Dermatomyositis may be heralded by muscular (weakness, tenderness, and pain), cutaneous (edema, eruption), or vasomotor (acrocyanosis or Raynaud-like) signs. The vulnerability of the muscles of the shoulder and pelvic girdle, the arms and thighs, and the neck is outstanding, and atrophy almost always develops in the affected groups. Implication of the vital striated musculature of the pharynx, larynx, thorax, and diaphragm constitutes the most serious complications of dermatomyositis. Cutaneous manifestations include edema, which may simulate closely that of scleredema, erythema, diffuse or patchy hyperpigmentation, sclerodermic thickening, lupus erythematosus-like efflorescence and poikiloderma atrophicans vasculare. Fever may be an accompaniment of dermatomyositis, although if it is present, it is usually of moderate grade. As noted before, fever is absent in the evolution of scleredema. Dermatomyositis follows a progressive course, often without remissions, to a certain stage, after which, if the patient survives, activity may cease. The disease terminates fatally in approximately one-half the cases. Recovery, when it occurs, is usually partial or is marked by residua such as muscular atrophy and incapacity as well as cutaneous sclerosis, pigmentation, and calcification.

It is doubtful if other conditions which may superficially resemble scleredema need be confused if concomitant features are properly appraised. Such diseases, listed here mostly for academic purposes, include myxedema, lymphedema, angioneurotic edema, hereditary trophedema, cardiorenal edemas, and elephantiasis. Sclerema neonatorum and edema neonatorum[3a,8] are rare, usually fatal diseases of newborn infants characterized by abnormalities in the subcutaneous tissues, and are accompanied by serious constitutional symptoms. Fox[5] has clearly differentiated these diseases from the benign, self-limited subcutaneous fat necrosis of newborn or young infants.

Treatment. Although claims for any recommended therapeutic regimen may rightfully be challenged in the light of the self-limited character of scleredema, we concur in the belief that the cutaneous picture can be influenced favorably by certain agents. We shall mention briefly our experience in the management of this series of cases. Since there is no interference, as a rule, with general health, restrictions need not be imposed upon the patient's activity. If feasible, foci of infection should be eradicated. It is our opinion that in 3 instances the disease was materially ameliorated by the removal of septic teeth or tonsils (this experience would suggest that sulphanilamide might possibly be deserving of trial). Thyroid was administered to several patients in an attempt to hasten involution by accelerating the peripheral circulation, but without impressive response. Our most valuable results were obtained, we believe, with induced fever, either alone or in combination with physiotherapeutic procedures. Fever was induced by means of typhoid vaccine injected intravenously and repeated at intervals for as long as visible improvement was forthcoming. Hypertherm sessions were employed in 2 instances. Softening and increased pliability of the skin of several patients could be demonstrated shortly after one or a few febrile bouts. Radiant heat, ultraviolet irradiation and judicious massage are effective auxiliary measures.

Comment. Precedence of scleredema by some acute infection is a nearly constant feature of the disease. Among such infections influenza, tonsillitis, measles, scarlet fever, mumps, otitis, erysipelas, and impetigo have been recorded. Then ensues a short interval lasting usually 2 or 3 weeks, during which the patient as a rule is free of symptoms, although vague aches and pains are sometimes experienced. Early in scleredema there may be an associated erythematous eruption, but this is exceptional and was not noted by any of our patients. In the majority of cases, the first abnormality which ushers in the disease is the peculiar deep edema and stiffness in the posterior or lateral cervical region. This change extends upward to include the adjacent skin of the neck, face and scalp, and downward over the shoulders, arms, trunk and, in fewer cases, the lower extremities. Nearly always the hands and feet remain unaffected. The tongue may be included in the involvement, as may also the general skeletal musculature.[2] Progression of the disease is usually complete in 2 or 3 weeks, although it sometimes requires a longer interval, and the condition, once established, remains stationary for a variable time, generally a period of several months, before involution begins. Depending on the extent of involvement, the patient may experience limitation of movement of the extremities, slight respiratory embarrassment, immobility of facial expression, dysphagia and general weakness. The duration of the disease is inconstant; some cases have been reported in which the disease cleared within a few days; other instances of the disease

have persisted for many years. Atrophy does not result. Touraine, Golé and Soulignac were convinced that cutaneous infiltration sometimes persists almost indefinitely in circumscribed portions, and that therefore the idea that complete clearing is a criterion for cure of scleredema is fallacious. Recurrences following recovery, as well as residua in the form of indurated cutaneous regions, are probably not uncommon.

The nature of the process is still a mystery. Buschke considered the possibility that diffuse disease of the lymphatic vessels might be a factor in the pathogenesis of scleredema. Touraine and his associates also supported the theory of direct, although attenuated, infection. They contended that cutaneous infiltration commences in the zone of primary infection, and since this zone is generally pharyngeal, the first appearance occurs in the region of the lymphatic drainage in the neck. The involvement, according to them, progresses in a manner analogous to that of erysipelas. Some substantiation for this theory may possibly be interpreted from our Cases 3 and 5.

Touraine and his associates have proposed to catalog scleredema, scleroderma and dermatomyositis under the inclusive title of "extensive benign sclerodermiform cellulitis." This term would signify a special type of inflammation of the cellular tissues of the cutis and subcutis with occasional deeper extension to the fasciæ and muscles. The aforementioned authors placed great emphasis on certain superficial attributes which the three diseases share in common. But to us there is an inadequate factual foundation for the thesis of these investigators, which seems to be largely supported by anomalous, presumptively "transitional" forms, unifying this group of so-called dermatoscleroses. Gottron[7] and Grzybowski[9] also have discussed certain clinical and histologic relationships of dermatomyositis to scleredema.

Disease of the cutaneous nerves has been suggested as an etiologic possibility,[11] and the alleged relationship of scleredema to trophedema has been discussed recently by Helfand.[10] The existence of a diffusible toxin which acted on the collagen was postulated by Sellei.[17] Endocrine disease has been incriminated as a possible factor in scleredema,[3b] as it has, with as little justification, in numerous other dermatoses. A vague similarity of scleredema to myxedema might be conjectured on pathologic grounds,[15] and an analogy to the somewhat limited distribution of scleredema may doubtfully exist in localized myxedema. The relationship of the infiltrating material in scleredema to the mucin it appears to resemble must await further elucidation. Until more is known of the histochemical nature of the cutaneous alterations occurring in scleredema, speculation in regard to pathogenesis is fruitless.

Summary. An analysis is presented of the clinical and pathologic features of 15 cases of scleredema adultorum in which the patients

were observed at The Mayo Clinic. The distinctive involvement of tissue and benign course are described, and other qualities are surveyed which distinguish the disease from diffuse scleroderma and dermatomyositis. Our experience with various agents of treatment is summarized. Probably the involution of scleredema may be accelerated by certain therapeutic procedures, even though the exact nature of the morbid process is for the present unknown. Theories of pathogenesis are reviewed.

REFERENCES.

(1.) **Buschke, A.**: Berl. klin. Wchnschr., **39**, 955, 1902. (2.) **Buschke, A.**, and **Ollendorff, H.**: Med. Klin., **23**, 1406, 1927. (3.) **Ehrmann, S.**, and **Brünauer, S. R.**: (*a*) Sclerema neonatorum, in J. Jadassohn, Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, **8**, Pt. 2, 866, 1931; (*b*) Scleroedema adultorum (Buschke), Ibid., p. 875. (4.) **Epstein, N. N.**: J. Am. Med. Assn., **99**, 820, 1932. (5.) **Fox, H.**: Arch. Dermat. and Syph., **27**, 237, 1933. (6.) **Freund, H.**: Arch. f. Dermat. u. Syph., **161**, 92, 1930. (7.) **Gottron, H.**: Hautveränderungen bei Dermatomyositis, in Comptes rendus des séances, VIII^e Congrès International de Dermatologie et de Syphiligraphie, Copenhagen, Engelsen & Schrøder, p. 826, 1931. (8.) **Gray, A. M. H.**: Arch. Dermat. and Syph., **14**, 635, 1926. (9.) **Grzybowski, M.**: Arch. f. Dermat. u. Syph., **174**, 541, 1936. (10.) **Helfand, M.**: Arch. Dermat. and Syph., **37**, 809, 1938. (11.) **Hoffmann, E.**: Klin. Wchnschr., **2**, 963, 1923. (12.) **O'Leary, P. A.**: Arch. Dermat. and Syph., **37**, 430, 1938. (13.) **O'Leary, P. A.**, and **Nomland, R.**: Am. J. Med. Sci., **180**, 95, 1930. (14.) **O'Leary, P. A.**, and **Waisman, M.**: Arch. Dermat. and Syph. (in press.) (15.) **Reuter, M. J.**: Ibid., **24**, 55, 1931. (16.) **Rissom**: Arch. f. Dermat. u. Syph., **94**, 39, 1909. (17.) **Sellei, J.**: Dermat. Ztschr., **54**, 161, 1928. (18.) **Sweitzer, S. E.**, and **Laymon, C. W.**: Arch. Dermat. and Syph., **37**, 420, 1938. (19.) **Touraine, A.**, **Golé, L.**, and **Soulignac**: Ann. de dermat. et syph., **8**, 761, 1937.

THE LYSOLECITHIN FRAGILITY TEST.

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The commonest test for the fragility of the red blood cells is based on the use of various concentrations of hypotonic salt solution. That the same red blood cells may behave differently towards different lysins is not generally appreciated. Thus according to Ponder,[25] who stresses the so-called Rywosch series, the red cells of different species behave in diametrically opposite ways to solutions of saponin and to hypotonic solutions of sodium chloride. The reaction of abnormal red cells to different lysins has been but little studied. In the course of previous work with the presence of lysolecithin in the blood of various normal and abnormal conditions, the reaction of the abnormal red blood cells of congenital hemolytic jaundice was studied. It was soon recognized that the spherocytes of this disease were unusually fragile to this lysin and that this reaction might be of some importance in diagnosis.

Congenital hemolytic (spherocytic) jaundice is characterized clinically by anemia, increase in reticulocytes, enlarged spleen and the signs of increased blood destruction (icterus, increased bilirubinemia, increased excretion of pigment in the urine and feces). Three further symptoms call for particular attention, namely: 1, the spherocytosis of the erythrocytes; 2, the decreased resistance of the red cells to hypotonic solutions of sodium chloride; and 3, the evidence of inheritance.

Spherocytosis is due to a decrease of the mean cell diameter with simultaneous increase of the mean thickness diameter. This change of form is considered by most authors (Naegeli,[23] Gänsslen,[12] Haden[13]) as pathognomonic of congenital hemolytic jaundice. Thus Thompson[27] (1936) says: "The spherical microcytes . . . . are as pathognomonic of this disease as are the sickle cells in sickle-cell anemia." Naegeli terms the disease "globe-cell anemia"; Krumbhaar[17] calls it "spherocytic jaundice." On the other hand, von Boros,[3] Heilmeyer[15] and Dameshek and Schwartz[7] describe the presence of spherocytes in various conditions. The latter authors found that spherocytosis was common to various hemolytic syndromes and on the basis of clinical and experimental observations concluded that this abnormality of the red cells was due to the action of various hemolytic agents upon the erythrocytes.

Increased fragility of the erythrocytes to solutions of hypotonic saline has also been regarded since the time of Chauffard[5] (1907) as pathognomonic of this disease. Haden[13] pointed out the direct correlation between spherocytosis and decreased NaCl resistance. However, Gänsslen,[12] who studied more than 100 cases, stated that in more than 10% of the cases the hypotonic salt resistance was normal. Furthermore, hemolytic anemia of other types, completely distinct from congenital hemolytic jaundice, also showed increased saline fragility.

The evidence of inheritance is of importance in diagnosis. The disease frequently remains quite latent, however, and only with the most careful hematologic methods can deviations from the normal be ascertained (Paschkis,[24] Gänsslen[12]). Hemolytic anemia may occur in the course of other diseases as so-called symptomatic forms. These cases have been observed in association with various exogenous and endogenous toxic influences. In this group belong the cases of sepsis from gas bacilli and streptococci (Widal[27] and his school), Hodgkin's disease of the spleen (Holler,[16] Davidson,[8] Singer[26] *et al.*), lymphatic leukemia (Paschkis,[24] Klima[17]) and of lead poisoning (Davidson,[8] etc.).

In addition to these symptomatic cases, is the group of cases of acute hemolytic anemia without congenital or familial background, and without obvious cause. Widal, Abrami and Brulé[28] described these cases as acquired hemolytic icterus; Chauffard[5] and his coworkers demonstrated the presence of serum hemolysins in certain

of them; Lederer[19] described them as a "new" disease; and more recently Dameshek and Schwartz[7] noted the presence of isohemolysins and the dramatic effect of splenectomy. In all of these cases of non-congenital, acquired hemolytic icterus, spherocytosis and increased saline fragility may be prominent features.

The establishment of spherocytosis in a case of hemolytic anemia is of essential importance. This is done by direct examination of the stained smear, and, as Dameshek[6] has recently shown, by studies of rouleaux formation and of "cupping" and so on in fresh preparations. Calculation of the mean cell diameter, the mean cell volume and the mean thickness diameter of the erythrocytes, although valuable, is laborious. In view of the recent investigations of Dameshek and Schwartz,[7] which demonstrate conclusively that spherocytosis cannot be considered as pathognomonic of the *congenital* hemolytic type, a test which discriminates between the spherocytes of the congenital and of the other types would be of some value. This paper deals with such a test, which is based upon the reaction of the red cells to a substance called "lysolecithin" derived from blood serum. Elaboration of the method was stimulated by the studies of Bergenhem and Fåhraeus.[2]

The Researches of Bergenhem and Fåhraeus. Three years ago these Swedish investigators reported the discovery of a new hemolysin in normal blood. They found that if defibrinated or citrated blood was allowed to stand quietly for several hours at body temperature, characteristic changes were produced: 1, considerable retardation of the sedimentation rate of the erythrocytes; 2, a change from the biconcave to the *spherical* form; 3, a noticeable reduction of aggregation (rouleaux formation). These changes, they concluded, were due to a modification of the serum. They found that serum contained a lecithinase, which was capable of splitting a substance from the serum lipoids; adsorption of this latter substance by the red blood cells resulted in the above changes. This enzymatic process reached its maximum at a temperature of 42° C. and a pH of 7.2 and was inactivated at 56° C. The substance, formed in undisturbed blood at a temperature of 37° C., was found to be identical with the so-called lysolecithin. Lysolecithin is a definite chemical substance, which has received prominence in the study of the biologic effects of snake venom. Flexner and Noguchi[11] were the first to show that blood serum was necessary in the hemolysis of red blood corpuscles by cobra toxin; red cells washed free of serum were incapable of lysis. Kyes and Sachs[19] found that the hemolytic effect of cobra toxin was activated by the presence of lecithin without serum being present. Further experiments (Lüdecke,[21] Manwaring,[22] Delezenne and Ledebt[9]) elucidated the mechanism of the action of this toxin. In the venoms of the cobra, scorpions, and of bees a lecithinase is present which splits from the lecithin molecule the unsaturated fatty acid group. The resulting residue is the hemolyzing lysolecithin. Chemically,

this substance is characterized by insolubility in ether and by ready solubility in water or alcohol.

The globular or spherocytic form of the erythrocytes produced by the adsorption of serum lysolecithin is in all probability the forerunner of hemolysis. At a stronger concentration of lysolecithin, complete hemolysis of the erythrocytes occurs. The amount of lysolecithin in freshly prepared normal serum is fairly low, amounting on the average to about one-fourth of the concentration which results when the undisturbed serum is kept at 37° C. for 24 hours.

In congenital hemolytic jaundice the circulating erythrocytes are either partly or wholly spherocytic. Since a dilute solution of lysolecithin renders the normal disk-shaped erythrocytes spherocytic, but a more concentrated solution leads to hemolysis, the question arises whether in hemolytic jaundice, the spherocytic cells are not more readily hemolyzed by lysolecithin than are normal erythrocytes. In order to decide this question, it was necessary first of all to possess an exact process for the extraction of serum lysolecithin, as well as an accurate method for determining its quantity.

Methods. Lysolecithin is prepared as follows: *At least* 20 cc. of animal (horse or dog) or human serum are warmed at rest for 24 hours (incubator) at 37° C. in order to obtain a maximal quantity of lysolecithin. The serum is then precipitated with 10 times its quantity of 95% alcohol, filtered and the filtrate evaporated in a vacuum apparatus at room temperature to complete dryness. The residue is again dissolved in a little alcohol, mixed with 6 times its quantity of ether and placed in the refrigerator overnight. The precipitate contains the lysolecithin. After removing the ether and drying the precipitate the content of lysolecithin is determined.

For this determination its hemolytic power is used. The quantity that is to be ascertained is dissolved in 0.8 cc. of physiologic salt solution. From this basic solution a geometric series of dilutions is prepared in the usual manner by further dilution with physiologic solution of NaCl. An approximate 2% saline suspension of washed erythrocytes containing about 100,000 cells per c.mm. is taken up in leukocyte pipettes to the 1 mark and diluted with the various single dilutions of lysolecithin to the 11 mark. While hemolysis is taking place, the pipettes are set aside for 1 hour. With extremely weak concentrations of the lysin, the reaction may be facilitated by placing the pipettes in the incubator for the same period. The solutions are then examined in a hematocytometer. By determining the number of undissolved erythrocytes an exact measure of the degree of hemolysis is obtained. Hemolysis above 90% is regarded as complete. The evaluation of exactly equal quantities of lysolecithin with the same amount of normal human erythrocytes always gives similar results, as has been proved by numerous experiments. If heterogenous erythrocytes are used the results may be entirely different. This is best shown in Table 1, in which the hemolytic power of 2 equally large quantities of lysolecithin has been measured both with human and dog erythrocytes.

TABLE 1.—COMPARATIVE HEMOLYTIC EFFECT ON HUMAN AND DOG ERYTHROCYTES.

Amount of hemolysis in %.	Lysolecithin dilution.								
	1:2.	1:4.	1:8.	1:16.	1:32.	1:64.	1:128.	1:256.	1:512.
Human erythrocytes	+	+	+	+	−	−	−	−	−
	100	100	100	98	42	0			
Dog erythrocytes	+	+	+	+	+	+	+	−	−
	100	100	100	100	100	100	100	58	0

The table shows that dog erythrocytes are much less (8 times less) resistant to lysolecithin than human ones. The test may likewise be used in the differential diagnosis of various hematologic cases, particularly when there is a question of congenital hemolytic jaundice. Equal quantities of lysolecithin are tested against the same amount of both normal and questionably abnormal erythrocytes. The dried lysolecithin (ether residue) from at least 20 cc. of unmoved incubated serum is dissolved in 1.6 cc. of normal saline. The solution is divided in equal parts and from these initial solutions the geometric series of dilutions is prepared.

For smaller quantities of lysolecithin, the method may be modified still further. For this purpose the test is made in special pipettes that take just one-half the contents of the normal leukocyte pipettes. The amount of serum used for the lysolecithin extraction can thus be reduced to 10 cc. The dried lysolecithin for each test is dissolved in 0.4 cc. of normal salt solution.

Results. A. *Normal Cases.* As numerous tests (30 cases) have proved that normal human erythrocytes always show the same resistance towards lysolecithin, the resistance of the spherocytes of congenital hemolytic jaundice has been determined in comparison with the normal. In order to give clear expression to the results, the tests have always been made with a concentration of lysolecithin that gives complete hemolysis up to the dilution 1 to 8. Of the normal cases, all of which showed the same results, 6 cases are included in Table 2.

B. *Congenital Hemolytic Jaundice.* As Table 2 shows, the resistance of the red cells of congenital hemolytic jaundice to lysolecithin is definitely less than that of the normal ones: whereas the normal cases show at most incomplete hemolysis at a lysolecithin dilution of 1 to 16, the cells of congenital hemolytic jaundice showed complete hemolysis at this dilution and in some cases there was more or less incomplete hemolysis at a dilution of 1 to 32. One case (No. 9) showed complete hemolysis at 1 to 32 and a high degree of incomplete hemolysis at 1 to 64. These values are the more remarkable when it is considered that the lysolecithin fragility test is made with a *geometric* progression of dilutions rather than with an arithmetic one, as in the fragility test with hypotonic solutions of sodium chloride.

To characterize the cases the following may be added. Cases 1 to 3 all came from one family and showed the typical symptoms of congenital hemolytic jaundice. The same applies to Case 4, who was aware of the character of his illness and of its familial character. In Case 5 the hereditary features were poorly defined. The father of the patient had died of pneumonia at an early age and the mother could not remember any symptoms characteristic for hemolytic jaundice in her husband. The examination of the mother showed completely normal hematologic conditions. The patient (an only

TABLE 2.—LYSOLECITHIN RESISTANCE OF NORMAL AND SPHEROCYTIC ERYTHROCYTES OF CONGENITAL HEMOLYTIC JAUNDICE.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.						
				1:2.	1:4.	1:8.	1:16.	1:32.	1:64.	Result.
	Hypertension	Normal	0.45–0.30	+ 100	+ 100	+ 92	− 26	− 0	−	Normal
	Normal case	Normal	0.45–0.30	+ 100	+ 100	+ 92	− 22	− 0	−	Normal
	Diabetes	Normal	0.45–0.32	+ 100	+ 100	+ 97	− 34	− 0	−	Normal
	Normal case	Normal	0.45–0.28	+ 100	+ 100	+ 92	− 19	− 0	−	Normal
	Hypertension	Normal	0.45–0.30	+ 100	+ 100	+ 97	− 38	− 0	−	Normal
	Normal case	Normal	0.45–0.30	+ 100	+ 100	+ 95	− 23	− 0	−	Normal
1	Hemol. jaund., man aged 49 yrs.	Hb. 50 E. 2.9 Retic. 9.0%	0.60–0.30	+ 100	+ 100	+ 100	+ 91	− 28	− 0	De-creased
2	Hemol. jaund., daughter of Case 1, aged 20 yrs.	Hb. 60 E. 3.3 Retic. 11%	0.55–0.30	+ 100	+ 100	+ 100	+ 93	− 20	− 0	De-creased
3	Hemol. jaund., son of Case 1, aged 14 yrs.	Hb. 54 E. 3.0 Retic. 7.8%	0.55–0.30	+ 100	+ 100	+ 100	+ 98	− 56	− 0	De-creased
4	Hemol. jaund., man aged 42 yrs.	Hb. 90 E. 4.2 Retic. 8.4%	0.64–0.56	+ 100	+ 100	+ 100	+ 93	− 49	− 0	De-creased
5	Hemol. jaund., boy aged 17 yrs.	Hb. 64 E. 3.6 Retic. 8.2%	Normal 0.45–0.30	+ 100	+ 100	+ 100	+ 92	− 60	− 0	De-creased
6	Hemol. jaund., girl aged 12 yrs.	Hb. 70 E. 3.6 Retic. 18%	0.80–0.30	+ 100	+ 100	+ 100	+ 100	− 38	− 0	De-creased
7	Hemol. jaund., mother of Case 6	Hb. 82 E. 4.4 Retic. 2.6%	Normal 0.45–0.30	+ 100	+ 100	+ 100	+ 96	− 51	− 0	De-creased
8	Hemol. jaund., man aged 50 yrs.	Hb. 106 E. 4.9 Retic. 7%	0.76–0.04	+ 100	+ 100	+ 100	+ 92	− 75	− 35	De-creased
9	Hemol. jaund., son of Case 8, aged 14 yrs., splenect.	Hb. 95 E. 4.8 Retic. 0.2%	0.60–0.04	+ 100	+ 100	+ 100	+ 98	+ 90	− 55	De-creased
10	Hemol. jaund., dghtr. of Case 8, aged 6 yrs., splenect.	Hb. 90 E. 4.4 Retic. 0.4%	0.68–0.16	+ 100	+ 100	+ 100	+ 94	− 79	− 36	De-creased

child) presented the signs of hemolytic anemia and had a large spleen. The mean diameter of the erythrocytes was 6.9 μ. The resistance of the red cells against hypotonic salt solution, determined several times, was normal. Despite this, the lysolecithin fragility was a pathologic one. Case 6 is a girl of 12, who since $1\frac{1}{2}$ years has had a large spleen, moderate enlargement of the liver, slight icterus and symptoms of hemolytic anemia. The greatly increased fragility of her erythrocytes towards hypotonic salt solution, the marked reticulocytosis as well as the high degree of urobilinogenuria indicated a hemolytic jaundice. The lysolecithin reaction confirmed the diagnosis. The anamnesis concerning the hereditary conditions, however, proved quite negative. The history, clinical and hematologic examination of the parents and of 2 brothers and sisters showed totally normal conditions, except that the number of reticulocytes was slightly increased in the mother. In spite of *normal* saline fragility of the erythrocytes the mother showed a high pathologic lysolecithin reaction. Thus the hereditary connections were also established in this case. The last 3 cases are all members of one family. The 2 children were splenectomized 2 years previously, as an emergency measure for severe hemolytic crises. As the splenectomized cases also showed a pathologic lysolecithin reaction, 1 case giving the most pronounced reaction of these series, it must be assumed that the abnormal fragility of the erythrocytes towards the serum lysin remains unchanged after splenectomy, although the fragility to hypotonic solutions of sodium chloride is sometimes considerably altered.

C. *Acquired Hemolytic Anemia.* The results of the lysolecithin fragility test in the non-congenital types of hemolytic anemia are seen in Table 3.

Case 1 should be discussed in detail. This patient, aged 45, 18 years previously had cervical adenitis, which a biopsy proved to be tuberculous. Six years prior to her present illness a mediastinal tumor was discovered and treated with Roentgen rays. Three months before entering the hospital, she became very anemic (Table 3), and numerous spherocytes were present. There was slight jaundice and a firm spleen was readily palpable 2 fingers below the costal margin. The liver was not enlarged. A large mediastinal tumor was again demonstrated. There was no other lymphadenopathy. From the hematologic standpoint the diagnosis was thus hemolytic jaundice. Hemolysis of the red cells to hypotonic saline began at 0.6% NaCl. Despite this pathologic fragility of the erythrocytes, the lysolecithin fragility was twice completely normal. Because of these data, hemolytic jaundice, associated with Hodgkin's disease of the spleen, was assumed. Splenectomy revealed a typical porphyric spleen. After operation, the anemia at first improved and then changed its character to that of a hypochromic type. There was a slight though definite response to iron, but 5 months later large masses of cervical glands appeared and the patient shortly died.

The occurrence of hemolytic anemia in cases of Hodgkin's disease, although rare, has been described by various authors as I pointed

out in another paper in 1936. Holler and Paschkis[16] (1927) reported a similar case with increased saline fragility and which likewise was submitted to splenectomy because of the diagnosis of congenital hemolytic jaundice. The normal lysolecithin fragility in the case reported above, in association with an abnormal saline fragility, proved valuable in the differentiation of the symptomatic from the constitutional form of hemolytic jaundice.

TABLE 3.—LYSOLECITHIN RESISTANCE IN OTHER HEMOLYTIC ANEMIAS.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.					
				1:2.	1:4.	1:8.	1:16.	1:32.	Result.
	Normal case	Normal	0.45–0.30	+ 100	+ 100	+ 94	– 44	– 0	Normal
1	Hemolytic anemia, Hodgkin's disease of the spleen	Hb. 52 E. 1.8 Retic. 12.6%	0.60–0.35	+ 100	+ 100	+ 92	– 36	– 0	Normal
2	Hemolytic anemia, lymph. leukemia	Hb. 25 E. 1.1 Retic. 13.8%	0.60–0.28	+ 100	+ 100	+ 98	– 29	– 0	Normal
3	Hemolytic anemia, lymph. leukemia	Hb. 34 E. 1.77 Retic. 8.3%	0.72–0.28	+ 100	+ 100	+ 100	– 55	– 0	Normal
4	Pernicious anemia	Hb. 50 E. 1.6 Retic. 1%	0.45–0.30	+ 100	+ 100	+ 91	– 27	– 0	Normal
5	Pernicious anemia	Hb. 40 E. 1.8 Retic. 0.3%	0.45–0.30	+ 100	+ 100	+ 94	– 32	– 0	Normal
6	Pernicious anemia	Hb. 30 E. 0.94 Retic. 0.7%	0.45–0.30	+ 100	+ 100	+ 100	– 39	– 0	Normal

CASE 2, a woman, aged 50, showed marked pallor several weeks before admission to the hospital. Examination showed a subicteric patient with a high degree of hemolytic anemia. The spleen was considerably enlarged, but there was no peripheral lymphadenopathy. The white cell count was 11,500 (88% small lymphocytes). The platelets were greatly reduced. Occasional nucleated red cells were seen, together with many small, dense-appearing microcytes (spherocytes). Sternal puncture revealed well-marked lymphoid infiltration of the bone marrow. Fragility of the red cells was increased to 0.6% of hypotonic saline, but the lysolecithin fragility was normal. The diagnosis of subleukemic lymphatic leukemia with symptomatic hemolytic jaundice was made.

CASE 3 showed a similar picture. A man, aged 70, showed a hitherto unrecognized chronic lymphatic leukemia which at the time of hospital admission was associated with acute hemolytic anemia. There was slight icterus, highly positive Van den Bergh reaction in the serum and increased

urobilinogen in the urine. Leukocytes count was: 142,500 of which 92% were mature lymphocytes. Most of the red cells were spherocytes; again the lysolecithin resistance was normal, but the saline fragility was greatly increased.

In 3 cases of pernicious anemia (Cases 4 to 6) with a typical blood picture and excellent response to liver treatment the lysolecithin fragility was normal.

Experiments have thus far indicated that the spherocytes of congenital hemolytic jaundice have a considerably reduced resistance towards lysolecithin, whereas the similarly morphologic spherocytic erythrocytes of other types of hemolytic anemias show a normal reaction to this lysin.

D. *Sickle-cell Anemia.* In this peculiar congenital condition, which is generally classified as a hemolytic disease, a considerably increased resistance to lysolecithin was observed in 2 of 3 cases. Marked sickling was demonstrable in fresh preparations of the blood of all 3 cases. Hemolysis in hypotonic saline began at a normal level (0.46 to 0.42%) but complete hemolysis was present only at 0.04%, an indication that some of the cells were very resistant to hypotonic salt solution. This fact was recently emphasized by Diggs and Bibb[10] who explain the increased resistance of the cells in sickle-cell anemia by the ability of these erythrocytes to alter their shape without placing their membranes under sufficient tension to cause hemolysis. More recent studies, particularly by Barrett,[1] have demonstrated that the most resistant cells have the general appearance of a target. It is possible, as Barrett points out, that these cells are the direct opposite of the spherocyte in regard particularly to thickness, and therefore most resistant to various lysins.

There is again, however, a lack of complete parallelism between the resistance of cells in sickle-cell anemia towards hypotonic NaCl and lysolecithin. Thus the erythrocytes of Case 3 presented a normal lysolecithin fragility although the presence of saline resistant cells in this case could be demonstrated.

E. *Chronic Non-hemolytic Jaundice.* In 3 of 6 cases of chronic non-hemolytic jaundice an increased resistance to lysolecithin was found. Two of these cases of chronic non-hemolytic jaundice had cirrhosis of the liver with long-standing icterus. The third case had a cancer of the pancreas with obstructive jaundice lasting for 7 weeks. The saline fragility in these cases was normal. In other cases of chronic non-hemolytic icterus both the lysolecithin and the saline fragility tests were normal. In a few cases, the saline fragility was decreased, although the lysolecithin test was normal. That the biochemical structure of the erythrocytes undergoes changes in chronic jaundice (pachydermia of the erythrocytes) has been known for a long time. Since Chanel[4] (1880) and others it has been accepted that the saline fragility of the erythrocytes is not infre-

quently decreased in obstructive jaundice. Barrett[1] has pointed out that "target" cells are seen frequently in the following conditions: sickle-cell anemia, where they have been first described by Haden and Evans,[14] and after splenectomy severe hepatic disease, particularly with obstructive jaundice.

TABLE 4.—LYSOLECITHIN RESISTANCE IN SICKLE-CELL ANEMIA AND IN CHRONIC NON-HEMOLYTIC JAUNDICE.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.					
				1:2.	1:4.	1:8.	1:16.	1:32.	Result.
	Normal case	Normal	0.48–0.30	+ 100	+ 100	+ 100	– 27	– 0	Normal
1	Sickle-cell anemia	Hb. 53 E. 2.7	0.42–0.04	+ 95	– 70	– 20	– 0	–	Highly increased
2	Sickle-cell anemia	Hb. 61 E. 4.9	0.46–0.04	+ 94	– 75	– 40	– 0	–	Highly increased
3	Sickle-cell anemia	Hb. 43 E. 1.9	0.46–0.04	+ 100	+ 100	+ 92	– 48	– 0	Normal
4	Chronic icterus, liver cirrhosis	Hb. 84 E. 4.5	0.44–0.28	+ 100	+ 100	– 65	– 0	–	Increased
5	Chronic icterus, liver cirrhosis	Hb. 92 E. 4.8	0.46–0.34	+ 100	+ 100	– 72	– 20	– 0	Increased
6	Chronic jaundice, Ca. pancreas	Hb. 91 E. 4.4	0.42–0.22	+ 100	+ 94	– 55	– 0	–	Increased

Discussion. The results thus far obtained demonstrate conclusively that the mechanism of lysolecithin hemolysis is different from that of NaCl hemolysis. Though the mechanism of NaCl hemolysis is still not entirely clear, we may assume that in consequence of osmotic differences there first occurs swelling and then bursting of the cell. On the basis of measurements of the cell diameter, Haden[13] demonstrated that normal erythrocytes show an increasing tendency to assume a spherical shape when submitted to decreasing concentration of NaCl.

As Bergenhem and Fåhraeus have demonstrated, lysolecithin likewise leads to spherocytosis, but by a different mechanism. The lysin is apparently directly adsorbed by the cell membrane. The normal disk-shaped erythrocytes are first made spherocytic by lysolecithin before hemolysis takes place. They thus require for complete hemolysis a larger quantity of lysolecithin than the already spherocytic cells of the congenital hemolytic jaundice.

This hypothesis does not explain the fact that definite spherocytes

in conditions other than the *congenital* type of hemolytic jaundice behave in a normal manner to lysolecithin. As Dameshek and Schwartz[7] have recently pointed out, spherocytosis is found in various hemolytic conditions, and is by no means pathognomonic of the familial form of hemolytic anemia. These authors produced spherocytosis of various degrees experimentally in guinea pigs by injecting anti-guinea pig hemolytic serum. These spherocytes also showed an increased saline fragility. The conclusion was reached that spherocytosis was due to the activity of hemolysins and not to an abnormal anatomic peculiarity or to a disturbed formation of cells in the bone marrow. Since increased fragility is a function of the increased thickness of the red cells, it is dependent on the same cause. The conclusion was also advanced that the various hemolytic syndromes were all due to hemolysins, possibly of different types and present in different amounts, functioning slowly in some cases and violently in others. They felt that various blood pictures of the hemolytic anemias, *viz.*, anemia, spherocytosis, increased fragility, were in all probability due to the effects of the varying activity of hemolysins.

Spherocytosis may thus be considered as the morphologic expression of a change in the erythrocytic structure due to the action of different kinds of hemolytic agents. It is a forerunner of hemolysis. As the various hemolysins are of quite different nature, one should expect that the resultant physico-chemical alterations in the structure of the cells might differ. The abnormal resistance of the spherocytes to lysolecithin in congenital hemolytic jaundice, as opposed to that in the acquired types, may therefore be explained by varying alterations in the cell structure, caused by chemically different substances. According to this hypothesis spherocytes, although morphologically similar, may be entirely different from the physico-chemical standpoint.

Although the exact mechanism of lysolecithin hemolysis cannot be explained, the practical importance of the use of lysolecithin in the study of erythrocyte fragility need not be influenced by this fact. The examination of the fragility of red blood corpuscles towards both hemolytic agents may be of value in the often difficult diagnosis of hemolytic anemias, as well as for the demonstration of an hereditary tendency. The chief disadvantage in the use of lysolecithin is that it is not readily available. This disadvantage is, however, more than offset by the possibility of a better differentiation of otherwise very similar clinical pictures.

Summary. 1. Bergenhem and Fåhraeus demonstrated that normal blood serum contains a hemolytic substance called "lysolecithin." In sufficiently high concentration complete hemolysis of red blood corpuscles occurred, whereas lesser concentrations of lysolecithin resulted in the development of spherocytosis.

2. A method is described for the extraction of lysolecithin from serum and for quantitative measurement of its hemolytic power. Lysolecithin, when extracted from the serum, may be used as a means of testing red cell fragility.

3. The spherocytes of congenital hemolytic jaundice are much less resistant towards this lysin than normal erythrocytes. This decreased resistance of the erythrocytes is occasionally one of the few demonstrable symptoms of latent forms of congenital hemolytic jaundice.

4. In the spherocytosis of various acquired and symptomatic types of hemolytic icterus, the lysolecithin fragility is normal although the saline fragility is definitely altered.

5. Certain cases of sickle-cell anemia and of chronic non-hemolytic jaundice show an increased resistance to lysolecithin.

6. The lack of parallelism in the resistance of various types of erythrocytes to lysolecithin and to hypotonic salt solution indicates that the mechanism of hemolysis by these hemolytic agents is a different one.

7. As Dameshek and Schwartz have pointed out, spherocytosis may be considered as the morphologic expression of an alteration in the structure of erythrocytes due to the action of different types of hemolytic substances. It is a forerunner of hemolysis. Since the spherocytes of congenital hemolytic jaundice and of various acquired types show a different susceptibility towards lysolecithin, the cell structure of these cells must vary. In other words, spherocytes, although morphologically similar, may be quite different physiologically.

REFERENCES.

(1.) **Barrett, A. M.**: J. Path. and Bact., **46**, 603, 1938. (2.) **Bergenhem, F.**, and **Fåhraeus, R.**: Ztschr. Exp. Med., **97**, 555, 1936. (3.) **von Boros, L.**: Erg. Inn. Med. u. Kdheilkd., **42**, 635, 1932; **12**, 255, 1928. (4.) **Chanel, A.**: Quoted by Naegeli.[23] (5.) **Chauffard, A.**: Sem. Méd., **27**, 25, 1907. (6.) **Dameshek, W.**: New England J. Med., **221**, 1009, 1939. (7.) **Dameshek, W.**, and **Schwartz, S. O.**: Ibid., **218**, 75, 1938; Am. J. Med. Sci., **196**, 769, 1938. (8). **Davidson, L. S. P.**: Quart. J. Med., **25**, 542, 1932. (9.) **Delezenne, C.**, and **Ledebt, S.**: Compt. rend. Acad. de Sci., Paris, **152**, 790, 1911; **153**, 81, 1911; **155**, 1101, 1912. (10.) **Diggs, L. W.**, and **Bibb, J.**: J. Am. Med. Assn., **112**, 695, 1939. (11.) **Flexner, S.**, and **Noguchi, H.**: J. Exp. Med., **6**, 277, 1902. (12.) **Gänsslen, M.**: Klin. Fortbildg., Berlin, Urban & Schwarzenberg, 1936. (13.) **Haden, R. L.**: Am. J. Med. Sci., **188**, 441, 1934. (14.) **Haden, R. L.**, and **Evans, F. D.**: Arch. Int. Med., **60**, 133, 1937. (15.) **Heilmeyer, L.**, and **Albus, L.**: Deutsch. Arch. f. Klin. Med., **178**, 89, 1936. (16.) **Holler, G.**, and **Paschkis, K.**: Wien. Arch. Inn. Med., **14**, 149, 1927. (17.) **Klima, R.**: Ibid., **26**, 277, 1935. (18.) **Krumbhaar, E. B.**: J. Am. Med. Assn., **107**, 1739, 1936. (19.) **Kyes, P.**, and **Sachs, H.**: Berl. klin. Wchnschr., **57**, 83, 1903. (20.) **Lederer, M.**: Am. J. Med. Sci., **170**, 500, 1925; **179**, 228, 1930. (21.) **Lüdecke, H.**: Quoted by Bergenhem and Fåhraeus.[2] (22.) **Manwaring, W. H.**: Ztschr. Immun. Forschg., **6**, 513, 1910. (23.) **Naegeli, O.**: Blutkrankh. u. Blutdiagnostik, 5th ed., Berlin, Julius Springer, 1931. (24.) **Paschkis, K.**: Ztschr. f. klin. Med., **105**, 301, 1927. (25.) **Ponder, E.**: The Mammalian Red Cell and the Properties of Hæmolytic Systems. Protoplasmamonographien VI., Berlin, Gebrüder Borntraeger, 1934. (26.) **Singer, K.**: Med. Klin., **32**, 179, 1936; Wien. Arch. f. inn. Med., **31**, 59, 1937. (27.) **Thompson, B. P.**: J. Am. Med. Assn., **107**, 1776, 1936. (28.) **Widal, F.**, **Abrami, F.**, and **Brulé, M.**: Arch. des mal. du coeur, **1**, 193, 1908.

NEW INDEXES DEMONSTRATING THE DEGREE OF ANISOCYTOSIS IN HUMAN BLOOD.

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The calculation of the average diameter of red blood cells enters into the routine of hematologic examinations, due to the considerable importance of the size of these cells in the classification of the anemias. For variations in size of the red blood cells in a given case, "anisocytosis" has been the only word used to express this condition. We propose in this paper the use of new hematologic indexes, denoting the quantitative and qualitative value of anisocytosis.

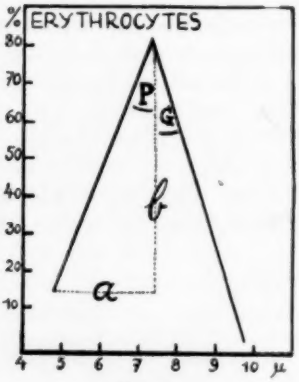

Fig. 1

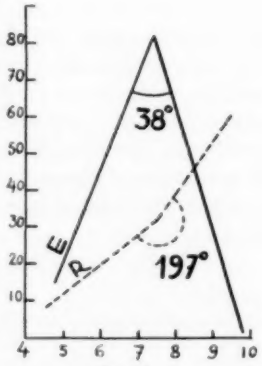

Fig. 2

Fig. 1.—Graphic illustrating method of calculation.
Fig. 2.—Graphic established on the 2d day of observation of a case of pernicious anemia during an anisocytic crisis.

Technique. On a glass slide 2 drops of the blood to be examined are mixed with 1 drop of 1% brilliant cresyl blue in Ringer solution. A cover glass with ground polished edges is used in making films of this mixture, which are allowed to dry, and then treated with either Wright's stain or that of the May-Grünwald-Giemsa combination. Thus one obtains preparations showing clearly the contour and normal size of the reticulocytes as well as of the erythrocytes.

Calculation. The average diameter of 300 erythrocytes is first established, and the results obtained are placed into three groups. The first, microcytic, comprise the cells of less than 6 μ. The second here considered as normocytic varies from 6 to 8.3 μ, whereas the third group, macrocytic, includes the cells larger than 8.3 μ. The average is thus calculated for each division by the following method. If in the second group the erythrocytes are measured and their diameters found to be 6.3 μ, 7.2 μ and 8.2 μ,

the number of the erythrocytes of each is multiplied respectively by 6.3, 7.2 and 8.2. The sum of these three multiplications is then divided by the total number of the erythrocytes pertaining to the second group. The result obtained gives the average diameter of the group. From the

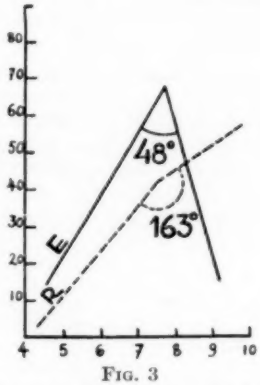

FIG. 3

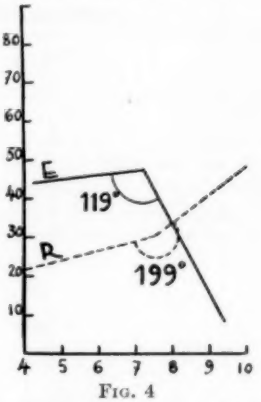

FIG. 4

FIG. 3.—Graphic established on the 5th day of observation of a case of pernicious anemia during an anisocytic crisis.

FIG. 4.—Graphic established on the 12th day of observation of a case of pernicious anemia during a microcytic crisis.

above, it is easy to determine 3 points graphically by inscribing on the abscissa the average diameters of the 3 groups, and on the ordinate, the percentages of the red blood cells. In the example graphically demonstrated, 15% of the cells belonged to the first group with an average diam-

FIG. 5

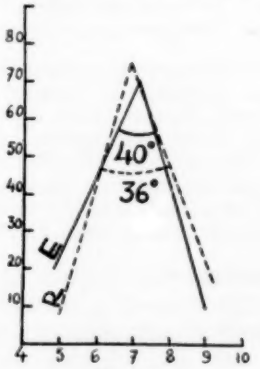

FIG. 6

FIG. 5.—Graphic established on the 16th day of observation of a case of pernicious anemia, *i. e.*, 4 days after the beginning of the treatment.

FIG. 6.—Graphic established on the 21st day of observation of a case of pernicious anemia, *i. e.*, 9 days after the beginning of the treatment.

eter of 4.8 μ, 82% to the second group with an average diameter of 7.4 μ, and 3% to the third group with an average diameter of 9.8 μ. The total angle formed by the two convergent lines represents the quantitative value of anisocytosis. By a vertical line drawn from the summit, this angle is

divided into angle P expressing the microcytic variation; and angle G denoting the macrocytic variation. The partial angles thus represent the qualitative value of anisocytosis. These various angles may be easily represented by their tangents according to the rules of trigonometry.

$$\text{Hence: } Tg.P = \frac{a}{b} = \frac{\text{difference of the average diameters}}{\text{difference of the percentages}} = \frac{7.4 - 4.8}{8.2 - 1.5} = \frac{2.6}{6.7} = 0.38.$$

By employing trigonometry tables, there is immediately obtained a more concrete value, expressed in degrees, in which the Tg. P. 0.38 corresponds to an angle P of 21 degrees. In the case represented in Figure 1 the Tg. G = 0.30 and the angle G = 17 degrees. Thus the total angle is 38 degrees. Needless to say, the calculation of these indexes is not necessarily determined graphically: the difference between the average diameters of the groups (a) and between the percentages of the blood cells (b) are supplied

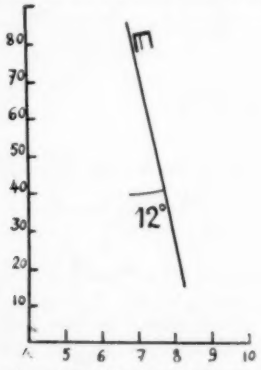

FIG. 7.—Graphic established on the 54th day of observation of a case of pernicious anemia at the apparent recovery.

by the measurements themselves, and the numbering of the 300 erythrocytes. A scheme has been given here only to make the explanation clearer. The same indexes (angle P, angle G, and the total angle) may be established for the reticulocytes. In this case the measurements are made on 100 reticulocytes. The values of these indexes are more outstanding for the reticulocytes than for the erythrocytes, in view of the fact that often even the angle G becomes obtuse. In this case the tangent is calculated on the supplementary angle and its value is negative.

Application. In order to demonstrate better the usefulness that the new anisocytic indexes determine, we add here the example of a classical pernicious anemia studied during the crisis on the 2d and 5th day of observation (1,720,000 R.B.C., megalocytosis, Plummer Vinson syndrome) as well as on the 12th day, during a microcytic crisis which determined the use of the liver extract treatment. A response to this treatment was demonstrated as early as the 16th and 21st days, while the 54th day corresponded with complete recovery from the attack (4,800,000 R.B.C.).

In the case of pernicious anemia that we have chosen as an example the figures are very striking. The improvement is manifested at the same time as (P + G) diminishes on the 16th day,

i. e., 4 days after the beginning of the treatment. The recovery is complete on the 54th day with a slight angle G for the erythrocytes, while the reticulocytes are too rare to allow a determination.

TABLE 1.—ANISOCYTOSIS VALUES IN A CASE OF PERNICIOUS ANEMIA.

Day.	Size.	Micro.	Normo.	Macrocytic.	Tg. P.	Tg. G.	Angle P.	Angle G.
2d	Eryth.	(4.8)	(7.4)	(9.8)				
		15%	82%	3%	0.38	0.3	21°	17°
	Retic.	(4.5)	(7.5)	(9.5)				
		8%	32%	60%	1.26	−0.71	52°	145°
5th	Eryth.	(4.6)	(7.7)	(9.3)				
		17%	68%	15%	0.6	0.3	31°	17°
	Retic.	(4.4)	(7.5)	(9.8)				
		3%	41%	56%	0.84	−1.53	40°	123°
12th	Eryth.	(4.3)	(7.2)	(9.4)				
		44.5%	45.6%	9.6%	26.00	0.61	88°	31°
	Retic.	(4.0)	(7.5)	(10.0)				
		22%	30%	48%	4.1	−1.38	76°	123°
16th	Eryth.	(4.4)	(7.6)	(9.7)				
		6%	70%	24%	0.5	0.45	27°	24°
	Retic.	(5.4)	(7.7)	(9.7)				
		3%	71.4%	25.6%	0.33	0.43	18°	23°
21st	Eryth.	(4.8)	(7.2)	(9.0)				
		19.3%	71.5%	9.3%	0.45	0.28	24°	16°
	Retic.	(5.0)	(6.9)	(9.2)				
		8%	76%	16%	0.27	0.38	15°	21°
54th	Eryth.	0	(7.7)	(9.2)				
			85%	15%	0	0.21	0°	12°

The numbers in parentheses above the numbers indicating the percentages express the average diameters of the three groups.

The quantitative value of the anisocytosis is expressed by the total of the angles P and G.

	2d day.	5th day.	12th day.	16th day.	21st day.	54th day.
Erythrocytes . .	38°	48°	119°	51°	40°	12°
Reticulocytes . .	197°	163°	199°	41°	36°	0°

Summary. 1. Three new hematologic indexes are introduced which by the simple calculation of the diameters of the blood cells and the recording of the latter in three groups according to their size, allow a numerical value to be given to anisocytosis.

The tangents P and G and the angles P and G demonstrate the qualitative value (micro- and macrocytic) of anisocytosis. The sum of the tangents or angles P and G represent the quantitative value of the same. The latter index goes down at the same time as anisocytosis lessens and approaches 0° in the normal blood.

2. The same indexes may be established on 100 reticulocytes. These obtained are still more outstanding than those for the erythrocytes.

THE INHIBITING EFFECT OF SNAKE BLOODS UPON THE HEMORRHAGIC ACTION OF VIPER VENOMS ON MICE.

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Previous investigators have established the fact that venomous snakes are not susceptible to large amounts of their own or closely related venoms. This observation led to the inquiry as to whether any protection was afforded by snake blood against the action of snake-venom. It was ascertained by direct experimentation that snake blood itself when injected into a warm-blooded animal was toxic, causing death after a period of increasing weakness terminating with convulsions. This finding confirmed the work of previous writers.[1,2,4a,5] These experiments, however, have led to the additional observation of a phenomenon, which it is believed has not as yet been described. It consists in the inhibition of the hemorrhage-producing action of pit-viper venoms, when a mixture of the latter and snake blood is injected.

Methods. The animals used were white mice weighing approximately 15 gm. each. The venoms used were those from rattlesnake (*crotalus adamanteus*), cotton-mouth moccasin (*agkistrodon piscivorus*), and fer de lance (*bothrops atrox*). Rattlesnake venom (the richest in hemorrhagin factor) was extracted at the laboratory from several snakes and pooled. It was dried immediately and used only on the same day as dissolved. The concentration of the venom dissolved in physiologic saline was 1/1000 (1 mg. of venom in 1 cc. of saline). The venoms of the moccasin and fer de lance were procured from snake farms in a dry form, and used on the same day as dissolved. The blood of snakes was obtained by decapitation and allowing the blood to run into a beaker. The bloods of the rattlesnake and of the non-venomous king snake (*lampropeltis getulus getulus*) were used. In the case of the rattlesnake, the mouth was first taped with adhesive plaster to exclude the possibility of any admixture of venom with the blood. Where plasma was used, the blood was mixed with 3.8% sodium citrate, 1 part to 9 parts of blood; where serum was employed, the blood was defibrinated by shaking with glass beads. In both instances, the blood cells were discarded after separation by centrifugalization. Plasma and serum while standing were kept in refrigeration. Some of the bloods were dried as soon as obtained by freezing-high vacuum apparatus; and when ready for use, dissolved in physiologic saline in the same volume as the original bloods.

Due to significant variations in the individual resistance of mice toward rattlesnake venom, a definite minimal lethal dose could not be established; however, 0.25 mg. of the venom injected subcutaneously was found to be close to a lethal dose for mice in 1 to 2 hours.

Rapid lethal action was insured by the subcutaneous injection of 0.5 mg. Autopsies were performed by stripping the skin from the trunk and by opening the peritoneal cavity, and observing the degree of hemorrhage. All mice injected subcutaneously with venom alone showed intense and extensive hemorrhage throughout the subcutaneous tissues, while those injected intraperitoneally with venom exhibited the same intense hemorrhagic reaction in the serosa. The degrees of hemorrhage found in the tabulated experiments are indicated by the following symbols:

++++ = very widespread hemorrhage
+++ = much less extensive hemorrhage
++ = moderate hemorrhage (about 2 sq. cm. in area)
+ = slight hemorrhage
0 = no hemorrhage or minute hemorrhage at site of needle puncture

Experiments. The first experiments showed that both the blood of the king snake (a non-venomous snake) and the blood of the rattlesnake are toxic. Certain lethal dosages in both cases are 1 cc. when injected subcutaneously and 0.25 cc. when injected intraperitoneally. King snake plasma is the more toxic of the two, requiring smaller doses to produce death. Even when heated at 56° C. for ½ hour these bloods retain a great portion of their toxicity. Autopsies upon mice so injected revealed an absence of hemorrhages, thereby differing from those autopsied after an injection of venom alone.

Varying amounts of king snake and rattlesnake bloods individually were mixed with rattlesnake venom and injected, subcutaneously and intraperitoneally. In all the mice so injected, death resulted and autopsy showed that there was either an absence, or slight to moderate degree of hemorrhage, whereas those injected with venom alone displayed an intense and very widespread hemorrhagic reaction.

It was further noted that the age of the blood (*i. e.*, the time that it has been kept outside the body) played an important rôle in the degree of inhibition of the hemorrhagic factor of the venom. The blood was much more effective in its control of hemorrhages when it was allowed to stand 24 to 48 hours before using. Blood 2 days old was more protective against hemorrhage from venom than that 1 day old. Fresh blood and old blood (more than 4 days old) had a considerable lesser anti-hemorrhagic effect. Fresh plasma and serum, dried at once by freezing-high vacuum apparatus and then dissolved, after a few weeks, in saline in the same proportion as the original plasma or serum, appeared to retain its anti-hemorrhagic property, unless kept standing in solution for more than 2 days. Both heated king snake and rattlesnake bloods (heated to 56° C. for ½ hour) still possessed most of their protective properties against the hemorrhagic action of rattlesnake venom. It must be borne in mind that the bloods of individual snakes vary as to their physiologic effects. Some are more toxic than others; and some appear to have more of an anti-hemorrhagic factor. The presence of a lesser amount

of this anti-hemorrhagic factor in some snake bloods may account for some apparently conflicting results. It may safely be assumed, however, that all of these bloods have some protection against the hemorrhages produced by venoms. The variation is minimal when 2-day-old blood is used. Table 1 summarizes these results.

The blood and venom need not necessarily be injected together. It was found when venom was injected within one hour after the administration of plasma or serum that there was still inhibition of hemorrhages, but to a lesser degree.

The anti-hemorrhagic factor of rattlesnake blood is active not only against rattlesnake venom but also operates against the hemorrhagic action of other venoms, those of the moccasin and the fer de lance (Table 2).

The anti-hemorrhagic principle present in snake blood was not found in the sera of various warm-blooded animals (Table 3).

Comment. These experiments show that snake blood inhibits the hemorrhagic action of snake venom, without affecting the lethal factor. Whether the resultant death is caused by the toxins of the venom other than hemorrhagin, or by the toxic action of the snake blood, or by the combination of the two, has as yet not been determined. Phisalix and Bertrand[3,4b] believed that death was produced by the toxic substances in snake blood, which existed side-by-side with antitoxins. They stated that by heating the blood to 58° C. for 15 minutes these toxins were destroyed, but the antitoxic activity was preserved. However, the experiments showed that heated snake blood (56° C. for 30 minutes) retained its toxicity, contrary to the findings of Phisalix and Bertrand. It is possible that a complete neutralization may have occurred and that the resultant death was mainly caused by the toxins of snake blood.

The action of snake blood is quite different from immune serum containing antivenin. Antivenin,* a true antitoxin, protects not only against the hemorrhagin of snake venom but also against the death of the animal. One might suspect that the hemorrhage-protecting power of snake blood in these experiments could be explained by the presence of specific antibodies prevailing in the blood stream, with death the result of the toxic action of foreign blood proteins. However, the following points seem to indicate that this phenomenon is not that of a specific antibody reaction, but rather the result of a non-specific neutralization of venom hemorrhagins:

1. Since auto-antibodies have been observed only under very exceptional conditions (as in paroxysmal hemoglobinuria), it is very doubtful that the anti-hemorrhagic effect of rattlesnake serum against its own and homologous venoms is due to a specific antibody.

2. Immune sera (antivenins) against snake venoms are specific for the venoms for which they have been prepared; whereas, as far

* The antivenin, a polyvalent serum, for nearctic Crotalidæ was obtained through the courtesy of Mulford Biological Laboratories, Philadelphia, Pa.

TABLE 1.—THE RESULTS OF INJECTIONS OF VENOM ALONE AND THE INJECTIONS OF MIXTURES OF VENOM AND SNAKE BLOOD.

Type of snake blood.	Amt., cc.	Crotalus adamanteus venom, mg.	Admin.	Time of death.	Degree of hem.	Remarks.
0	0	½	s	20′–1 hr.	++++	Control
0	0	½	p	15′	++++	Control
0	0	¼	s	1–2 hrs.	++++	Control
0	0	¼	s	Lived	....	Control
Fresh R.S.S.	1/10	½	s	2–2½ hr.	++++	
Fresh R.S.P.	1/10	½	s	1½–2 hr.	++++	
Fresh R.S.S.	¼	½	s	2–3 hr.	some ++ some +++	
Fresh R.S.P.	¼	½	s	½–3 hr.	some + some +++	
Fresh R.S.S.	½	½	s	1–2½ hr.	some + some ++	Blood withdrawn from heart showed no hemolysis
Fresh R.S.P.	½	½	s	6 hr.	some + some ++	
1-day-old R.S.P.	1/10	½	s	2½ hr.	++	
1-day-old R.S.P.	¼	½	s	½–2½ hr.	sev. 0 occ. ++	
1-day-old R.S.S.	¼	½	s	1½ hr.	0	
1-day-old R.S.P.	½	½	s	1½ hr.	0	
1-day-old K.S.P.	½	½	p	20′	0	Venom injected ½ hr. after plasma.
1-day-old K.S.P.	½	½	s	½ hr.	0	
1-day-old K.S.P.	1	½	s	1½ hr.	0	
1-day-old R.S.P.	1/20	¼	s	2½ hr.	+	
1-day-old R.S.P.	1/10	¼	s	1 hr.	+	
1-day-old R.S.P.	¼	¼	s	½–1 hr.	0	
1-day-old R.S.P.	½	¼	s	1 hr.	0	
2-day-old R.S.P.	1/10	½	s	½–1 hr.	some + some ++	
2-day-old R.S.P.	¼	½	s	1–2 hr.	most 0 occ. +	
2-day-old R.S.P.	¼	½	p	½–6 hr.	most 0 occ. +	
2-day-old R.S.P.	½	½	s	½–1½ hr.	0	
2-day-old R.S.S.	½	½	p	½ hr.	0	
2-day-old K.S.P.	½	½	s	1–4 hr.	most 0 or + occ. ++	
2-day-old heated K.S.P.	½	½	s	1½–5 hr.	most 0 occ. +	
2-day-old heated K.S.P.	½	½	p	1 hr.	0	
3-day-old R.S.P.	1/20	¼	s	2 hr.	0	
3-day-old R.S.P.	1/10	½	s	Lived		
3-day-old R.S.P.	¼	½	s	½–6 hr.	0	
3-day-old R.S.P.	½	¼	s	3 hr.	0	
4-day-old heated R.S.P.	½	½	s	2½ hr.	+	
6-day-old R.S.S.	¼	½	s	1 hr.	+	
9-day-old heated K.S.P.	½	½	s	4½ hr.	+++	
Freshly dried R.S.S.	1/10	½	s	1½ hr.	++	Used same day as dissolved.
Freshly dried R.S.S.	¼	½	s	1 hr.	0	
Freshly dried R.S.P.	¼	½	s	15′	0	
Freshly dried R.S.S.	¼	½	s	2½ hr.	+	Used 1 day after dissolved
Freshly dried R.S.P.	¼	½	s	20′	+	
Freshly dried R.S.S.	¼	½	s	½ hr.	++	Used 4 days after dissolved
Freshly dried R.S.P.	¼	½	s	40′	++	

Abbreviations: R.S. = rattlesnake, K.S. = king snake, P = plasma, s = subcutaneous, p = peritoneal, S. = serum, hem. = hemorrhage.

All heated bloods were heated to 56° C. for ½ hour.

All dried bloods were dried on the same day as collected. They were kept in dry form for a few weeks and then dissolved and used after the periods of time indicated in the table.

as our findings go, snake sera protect against the hemorrhagic action of heterologous venoms. This observation can be reconciled with the assumption of specificity only by postulating a multiplicity of antitoxins in snake sera.

TABLE 2.—THE PROTECTIVE ACTION OF RATTLESNAKE PLASMA (R.S.P.) AGAINST THE HEMORRHAGIC ACTION OF OTHER VIPER VENOMS.

Amount of R.S.P.	Venom used.	Venom in mg.	Degree of hemorrhage.
0	Bothrops atrox	½	++++
0	Agkistrodon piscivorus	½	++++
¼ cc. (2-day-old)	Bothrops atrox	½	0
¼ cc. (2-day-old)	Agkistrodon piscivorus	½	0

Plasma and venom mixed immediately before subcutaneous injection.
All mice were killed and autopsied after 1 hour and 45 minutes.

3. Fresh snake plasma or serum is not as effective in its inhibition of hemorrhagic activity as is blood aged from 1 to 4 days, and rapidly loses this power. This would be an unusual finding for a specific antibody, although it does not exclude it.

TABLE 3.—THE LACK OF PROTECTIVE POWER OF VARIOUS BLOODS OF WARM-BLOODED ANIMALS AGAINST THE HEMORRHAGIC ACTION OF RATTLESNAKE VENOM.

Type of blood and amount in cc.	Crotalus adamanteus venom, mg.	Time of death, hrs.	Degree of hemorrhage.
Rabbit serum (2-day-old) ½	½	2	++++
Fresh human plasma ½	½	1¾	++++
Human plasma (3-day-old) ½	½	1¾	++++
Guinea pig serum (1-day-old) ½	½	1¾	++++
Horse serum (age unknown) ½	½	1	++++

Mixtures of blood and venom injected subcutaneously in mice.

Conclusions. 1. King snake and rattlesnake bloods protect against the hemorrhagic action of viper venoms, but do not prevent death.

2. The time that the snake blood has been kept outside the body plays an important rôle in its power to inhibit the hemorrhages caused by viper venoms.

3. The bloods of mammals are not protective against the hemorrhagic action of rattlesnake venom.

4. Evidence is cited supporting the idea that the action of snake blood in protecting against the hemorrhages produced by viper venoms is not identical to that afforded by antitoxin (antivenin).

5. The toxic and anti-hemorrhagic properties of snake blood are thermostabile, retaining them after heating to 56° C. for ½ hour.

6. Blood, both from venomous and non-venomous snakes, is toxic; but the resultant death, unlike that produced by viper venoms is not accompanied by hemorrhages.

REFERENCES.

(1) **Calmette, A.**: Venoms, Chap. 10, London, John Bale, Sons & Danielsson, Ltd., 1908. (2.) **Noguchi, H.**: Snake Venoms, Publication of Carnegie Inst. of Washington, 1909. (3.) **Phisalix, C.**: Compt. rend. Cong. Internat. de médécine, Moscou, **2**, 157, 1897 (Sect. 3). (4.) **Phisalix, C.**, and **Bertrand, G.**: (*a*) Compt. rend. Soc. de biol., vi-8–1894; (*b*) Compt. rend. d. l'Acad. d. sci., **121**, 745, 1895. (5.) **Welker, W. H.**, and **Marshall, J.**: J. Pharm. and Exp. Therap., **6**, 563, 1915.

THE SIGNIFICANCE OF THE OXIDATION OF SULPHANILAMIDE DURING THERAPY.*

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The detection of methemoglobin in the blood of patients treated with sulphanilamide[1,2,7,10,12,18,19,26] provides an important clue to the possible mechanism of action of the drug.[24] Since this abnormal pigment is formed from hemoglobin only by the action of strong oxidizing agents,[8] the opinion seems warranted that a rather powerful oxidizing agent is present during therapy. Sulphanilamide itself is not an oxidant and does not form methemoglobin outside the body.† It follows, therefore, that administration of the drug is accompanied by the constant formation of some substance capable of oxidizing hemoglobin to methemoglobin.

The problem, then, is whether such a substance can be formed from sulphanilamide. This may readily be accomplished[25] by exposing the drug‡ to the rays of an ordinary ultraviolet lamp in the presence of oxygen. Oxidation of sulphanilamide occurs in a minute or two.[13] The resulting violet blue solution, which probably contains several products, oxidizes hemoglobin to methemoglobin instantly.[12] During this second oxidation, the blue oxidizing solution turns brown. It is obviously important to know whether this brown pigment exists in sulphanilamide-treated patients' blood, indicating the occurrence *in vivo* of these oxidations. Evidence on this point has been difficult to obtain. However, by using the Hardy recording spectrophotometer§ at the Massachusetts Institute of Technology, we have shown that the blood of these patients contains a colored substance with spectral characteristics similar to those of the brown pigment formed when the blue photo-oxidation product oxidizes hemoglobin to methemoglobin *in vitro*.[12]

Additional evidence for the *in vivo* oxidation of sulphanilamide has come recently from Rosenthal's[27] observation that 1 to 3% of an oxidation product of the drug appears in the urine of sulphanilamide-treated patients.

Experimentally, there are many observations which indicate that when bacterial growth is suppressed by sulphanilamide, the

* Read at the Third International Congress for Microbiology, September 4, 1939.

† Unpublished experiments.

‡ The sulphanilamide is dissolved in water or dilute buffer (pH 7.3) in the optimal therapeutic concentration 10 mg. per 100 cc. or 1 to 10,000 and exposed in a thin layer in an open vessel.

§ Designed by Prof. A. C. Hardy,[16] this accurate, automatic machine utilizing photoelectric cells draws a smooth curve of the light transmitted through a sample from 400 to 700 μ.

drug itself is oxidized. Comparative studies of the growth of virulent β hemolytic streptococci in the presence and absence of sulphanilamide were made with Janeway.*[4,14] Chart 1 (Chandler and Janeway[4]) shows growth curves, with plate counts taken at 2-hour intervals, of cultures of β hemolytic streptococci with and without 10 mg. per 100 cc. sulphanilamide. It is striking that during the first 4 or 5 hours of growth, the sulphanilamide culture grows equally with the control. In other words, although the drug is in solution and is readily diffusible, no bacteriostasis occurs until the bacteria are in

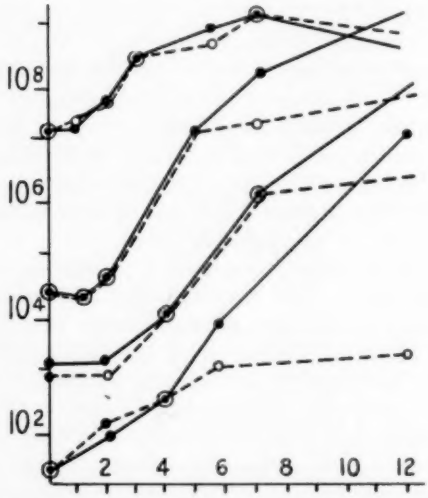


CHART 1.—EFFECT OF SULPHANILAMIDE ON GROWTH OF HEMOLYTIC STREPTOCOCCI IN VITRO.

Ordinate—logarithm of number of bacteria present. Abscissa—time in hours. Broken line represents medium with 10 mg. per 100 cc. sulphanilamide, solid line represents control medium without sulphanilamide. No bacteriostasis manifest during first 4 to 5 hours until logarithmic phase. Larger inocula give less or no bacteriostasis.

the logarithmic phase of rapid growth. If the assumption be made that the bacteria oxidize the drug to the potent oxidant, then by analogy with Dubos' experiments,[9b] vigorous oxidation would proceed only after the bacteria had entered the logarithmic phase of growth. That this actually occurs is fairly clear. Using bright platinum electrodes and a potentiometer, Warren[31] and the writer working independently[14] found an elevated oxidizing electrode potential in hemolytic streptococcus cultures containing sulphanilamide during the logarithmic period (Chart 2*A*). This elevation was maintained in cultures containing the drug, whereas in control cultures the usual reducing conditions marked by falling potentials

* Some experiments reported in Ref. 14, others to be published with Janeway.

prevailed.[3,15] These results suggested the formation of an oxidant in the sulphanilamide media. Furthermore, since oxidation of sulphanilamide to a strong oxidant requires the participation of oxygen,[13] removal of oxygen at the beginning of the experiment should prevent this chemical change and coincidentally, prevent bacteriostasis. This is in fact the case. With six strains of Group A hemolytic streptococci,[30] if removal of oxygen and reduction are complete *before* inoculation,* bacteriostasis by sulphanilamide is prevented.†

The assumption that oxidizing conditions are necessary for bacteriostasis is further supported by the low threshold of inoculum size. While increasing sulphanilamide effect with decreasing inocula is a predictable occurrence (as Chart 1 shows), when the relatively low inoculum limit of 100,000 organisms per cc. is exceeded no bacteriostasis can be detected, even with a large excess of sulphanilamide. Potentiometric comparison (Chart 2*B*) of the electrode behavior of small and large inocula shows that whereas the small inoculum permits longer maintenance of the elevated oxidizing potential, the large inoculum rapidly establishes reducing conditions inimical to oxidative reactions and oxidants.[14] In other words, there seem to be two antagonistic reactions: (*a*) the creation from sulphanilamide of an oxidant and its successful functioning; (*b*) the establishment of reducing conditions in the media by the metabolic activity of the bacteria. As the size of the inoculum is increased, reducing conditions prevail sooner and either greatly inhibit the oxidation of sulphanilamide or interfere with the oxidation reactions of the newly formed oxidant. Accordingly, it is evident that bacteriostasis can occur only when oxidizing conditions prevail over reducing conditions.

A parallel may be drawn from the clinical experience that sulphanilamide rapidly controls cases of septicemia, infections which take place in a well oxygenated environment, whereas it fails to show much effect against infections with similar organisms in closed cavities or abscesses where oxygen lack and intense reducing conditions prevail. Other factors may also play a rôle as Lockwood has pointed out.[22]

If this view is correct, it ought to be possible to augment the effect of the drug by favoring oxidation and by preventing reduction. As a matter of fact, simple aeration of the culture by agitation augments bacteriostasis. The next logical step is to preform an

* Technically this object cannot be accomplished by using the various types of hydrogen anaërobic jars, which will remove oxygen in the superambient atmosphere of the jar but fail to effect reduction of the media and bring about complete removal of oxygen before any sulphanilamide has been oxidized. Types 1, 6, 14, 18 and two strains that could not be typed were tested in 0.01% dextrose infusion broth or 20% horse serum neopeptone water. In the former, medium spontaneous reduction under vaseline sufficed; in the latter, it was necessary to add 0.1% neutralized cysteine[14] for complete reduction of the methylene blue oxygen indicator.

† Some experiments reported in Ref. 14, others to be published with Janeway.

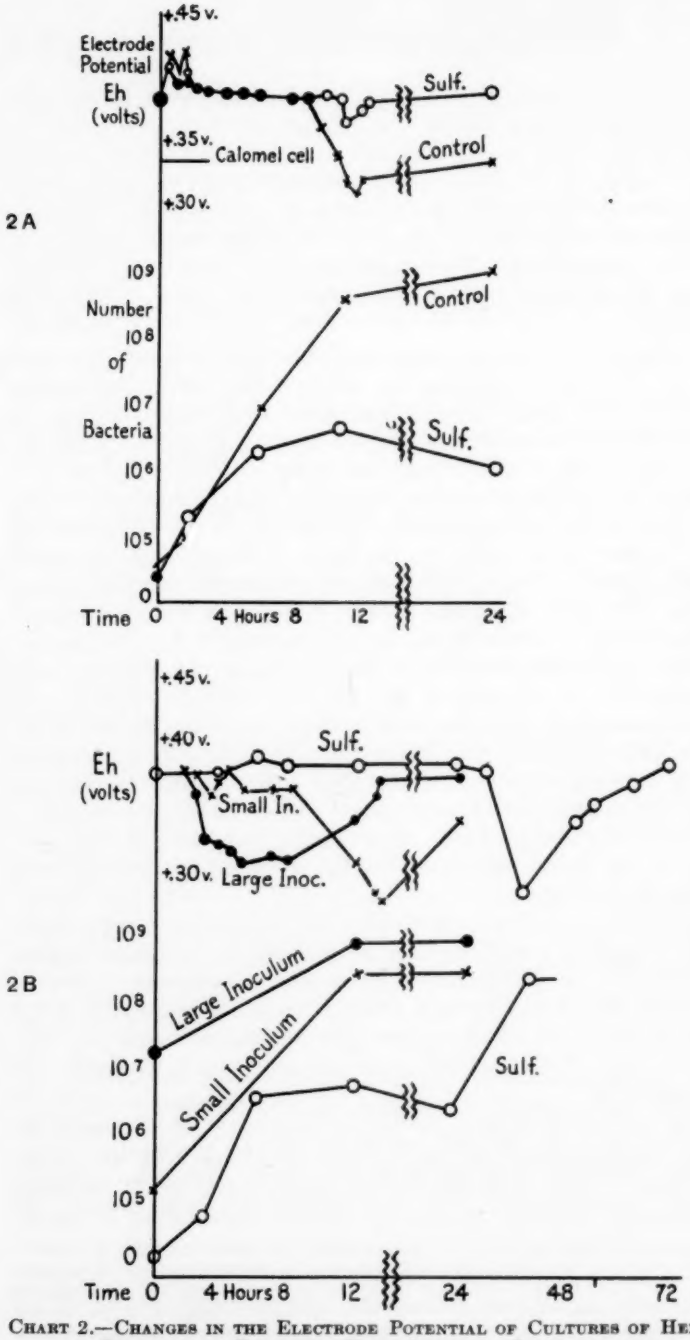
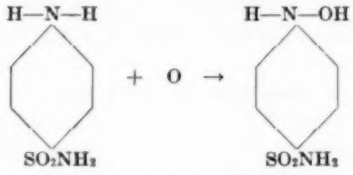


CHART 2.—CHANGES IN THE ELECTRODE POTENTIAL OF CULTURES OF HEMOLYTIC STREPTOCOCCI RESULTING FROM ACTION OF SULPHANILAMIDE.

Upper curves show electrode potential variations in control and sulphanilamide containing cultures. Lower curves show growth rate of these cultures. Electrode potential in sulphanilamide containing culture elevated during bacteriostasis while potential of control fell. When the sulphanilamide containing cultures finally grew out (Chart 2*B*) then the potential there also fell. Rapid fall of electrode potential in culture with large inoculum; delayed fall with small inoculum.

oxidant from the drug before use. This has been accomplished by Drs. Rosenthal and Bauer in Washington who very kindly supplied me with a sample. The first oxidation product of sulphanilamide is 4-hydroxylamino benzene sulphonamide, an unstable compound formed by introducing an atom of oxygen into the amino group without loss of hydrogen.* Like the photoxidation product†



of sulphanilamide, this sample of hydroxylamino sulphonamide oxidizes hemoglobin to methemoglobin and inactivates catalase. Hydroxylamino sulphonamide accomplishes immediate bacteriostasis, thereby completely eliminating the previously described initial growth period (Table 1). Furthermore, it gives more prolonged bacteriostasis possibly because there is more of the oxidant.

TABLE 1.—BACTERIOSTASIS WITH 4-HYDROXYLAMINO SULPHONAMIDE.

	Bacterial counts—colonies in thousands per cc.					
Interval.	Initial inoculum.	2 hrs.	4 hrs.	6 hrs.	8½ hrs.	18 hrs.
Control . . .	86	340	5700	..	350,000	++++
Sulphanilamide* .	86	440	5450	..	32,500	++++
Hydroxylamino sulphonamide* .	86	117	1000	..	25,000	++++
Control . . .	15	150	1000	25,000	86,000	++++
Sulphanilamide* .	15	140	1300	6,000	21,000	++++
Hydroxylamino sulphonamide* .	15	7	100	100	1,000	++++

* 10 mg. per 100 cc. in 0.1% dextrose beef heart broth. Strain: Group A hemolytic streptococcus H (Gay). Medium: 0.1% dextrose beef heart broth.

Recently, utilizing empyema fluid drawn and maintained under seal, it has been possible to demonstrate the marked bacteriostatic action of 4-hydroxylamino benzene sulphonamide in this physiological reducing anærobic environment where both sulphanilamide and sulphapyridine failed to elicit any bacteriostatic action.

At this point several questions arise. Has an oxidation product of sulphanilamide, or a diminution of sulphanilamide concentration, been detected chemically in cultures? (See addendum.) Special methods would be needed to detect hydroxylamino-sulphonamide under such conditions (see addendum). This substance is very

* *In vivo* or *in vitro* oxidation to the free radical by loss of an electron or loss of hydrogen may occur. This, too, would be an unstable, powerful oxidizing agent.

† This blue product has not been shown to be bacteriostatic probably because it is formed only in dilute solution and is rapidly reduced when added to media.[13]

unstable and it is unlikely that significant amounts of it could be present at any one time. Furthermore, estimations by the Marshall method[23] do not distinguish between sulphanilamide and the oxidant. The characteristic lability that interferes with the demonstration of such a substance during therapy may, however, be a very valuable attribute. Thus, instability of the oxidant might provide for a gentle throttling of bacteria rather than wholesale slaughter of both host cells and hostile cells. It might produce fractional rather than total methemoglobinemia.

The transitory existence and rapid destruction of such a substance in the test tube is supported by the following facts:[4] (*a*) sulphanilamide containing media in which bacteriostasis has occurred and in

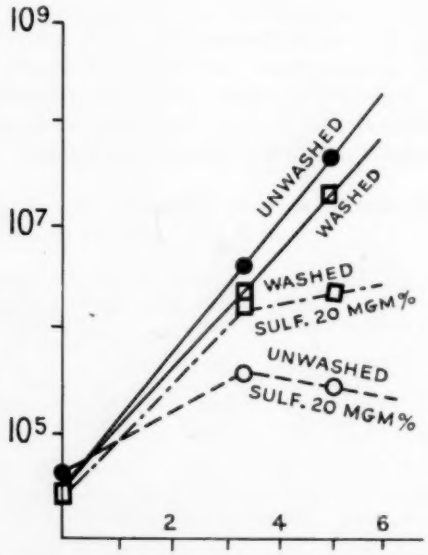


CHART 3.—ALTERATION OF HEMOLYTIC STREPTOCOCCI CAUSED BY SULPHANILAMIDE REVERSED BY WASHING.

Bacteria previously grown in media containing sulphanilamide show prompt bacteriostasis on subculture in sulphanilamide containing media (broken line). Washing reduces this effect, and subculture in sulphanilamide-free media (solid line) shows no bacteriostasis at all.

which the oxidant is presumably present, when freed of their bacteria, are no more bacteriostatic than fresh sulphanilamide media; (*b*) an inoculum composed of bacteria obtained from such sulphanilamide containing media during bacteriostasis, on subculture in fresh sulphanilamide media responds at once to the drug without the usual initial growth period; but (*c*) on subculture in sulphanilamide-free media, such bacteria grow entirely normally, showing no

sign of their erstwhile disability. On the other hand (*d*), if sulphanilamide-grown organisms are washed, they behave like ordinary bacteria in fresh sulphanilamide media, indicating at best only a loose binding between bacteria and the oxidant. Apparently this oxidation proceeds along with the normal bacterial metabolic oxidations at the surface of the bacteria, so that the oxidant formed may survive only long enough to function. The bacteria grown in sulphanilamide-containing media are reversibly altered and this reversal is prevented only by the continued action of sulphanilamide, which would seem to keep the reaction going to the right against a tendency toward reversal to the left (see Chart 3).

It is also of considerable importance that certain tissues aerobically induce the conversion of sulphanilamide to a methemoglobin-producing oxidant, as shown recently by Harris[17] with surviving liver or kidney tissue *in vitro* (see addendum). It should be emphasized that only a particular oxidation of sulphanilamide is effective: that in which the product formed is itself an oxidizing agent. This means that inactive sulphanilamide is transformed into a highly active agent by chemical legerdemain. If human tissues can transform sulphanilamide into the effective agent in the absence of infection, a rational basis exists for the use of sulphanilamide to forestall streptococcal infections as described by Coburn.[6]

Now of what use is an oxidant?* How may an oxidant inhibit bacterial propagation? These questions were answered long before the advent of sulphanilamide. Dubos clearly showed that oxidized substances inhibited growth and that reduction of these same substances favored growth.[9a] Fildes demonstrated that the same conditions governed the growth of anaerobes,[11] and Kligler and Guggenheim induced anaerobes to grow in the presence of oxygen by lowering the potential of the media.[21] Schmelkes,[28] and later Clark,[5] showed that the usual inhibitory halogen oxidizing compounds, even in large quantities, were ineffective provided the usual electrode potential of the bacterial cells was not elevated. The mechanisms involved have been elucidated by the studies of Clark and Hellerman[20,29] on isolated systems: enzymes such as papain, cathepsin and urease, and bacterial toxins and hemolysins are reversibly inactivated by oxidants and may be reactivated by reductants. The application of these facts to the present problem is that sulphanilamide bacteriostasis may rest upon the production of oxidizing conditions which serve to inactivate enzymes and inhibit bacterial growth; that sulphanilamide bacteriostasis is nullified by reducing conditions which reactivate enzymes and favor bacterial growth.

* Discussion by author at Am. Med. Assn. meeting, May, 1939, section on Pharmacy and Therapeutics (to be published).

Summary and Conclusions. The conclusion that sulphanilamide is oxidized during therapy is supported by these observations:

1. Complete, initial deprivation of O_2 interferes with bacteriostasis.

2. Increased oxygen availability magnifies bacteriostasis.

3. Reducing agents and large inocula, which rapidly reduce the potential, obliterate bacteriostasis despite excess of sulphanilamide.

4. The use of a preformed oxidant derived from sulphanilamide, 4-hydroxylamino sulphonamide,* eliminates the usual initial growth period before bacteriostasis appears and gives a more prolonged effect than sulphanilamide.

5. The occurrence of methemoglobinemia during therapy and the occurrence of an oxidation product* of sulphanilamide in the urine of treated patients confirm the view that an oxidant is produced in the blood or tissues of the patient.

* *Addendum.* This has since been similarly detected in a sulphanilamide-containing bacterial culture, in the product formed by ultraviolet irradiation of sulphanilamide and in the methemoglobin-forming oxidant produced by surviving liver and kidney tissue oxidation of sulphanilamide. The product of ultra-violet irradiation is significantly different from these in giving a positive Rosenthal test after treatment with alkali. Alkali decomposes 4-hydroxylamino sulphonamide which subsequently fails to show this test. A detailed report will be published separately on this point.

The writer wishes to express his gratitude to Dr. Hans Zinsser, of the Harvard Medical School, and to Prof. George S. Forbes, of the Harvard Chemical Laboratory, for their hospitality and encouragement while this work was in progress in their laboratories. To Drs. Reuben Ottenberg and Charles A. Janeway are due thanks for invaluable criticism and suggestions.

REFERENCES.

(1.) **Bensley, E. H.**, and **Ross, J. B.**: Canad. Med. Assn. J., **37**, 62, 1937. (2.) **Campbell, D.**, and **Morgan, A.**: Lancet, **2**, 123, 1939. (3.) **Cannan, R. K.**, **Cohen, B.**, and **Clark, W. M.**: U. S. Pub. Health Rep., Suppl., vol. **55**, 1926. (4.) **Chandler, C. A.**, and **Janeway, C. A.**: Proc. Soc. Exp. Biol. and Med., **40**, 179, 1939. (5.) **Clark, W. M.**: Harvey Lect., Ser. 29, p. 67, 1933–1934. (6.) **Coburn, A. F.**, and **Moore, L. V.**: J. Clin. Invest., **18**, 147, 1939. (7.) **Colebrook, L.**, and **Kenny, M.**: Lancet, **1**, 1279, 1936. (8.) **Conant, J. B.**, and **Pappenheimer, A. M., Jr.**: J. Biol. Chem., **98**, 57, 1932. (9.) **Dubos, R.**: (*a*) J. Exp. Med., **49**, 559, 1929; (*b*) Ibid., **50**, 143, 1929. (10.) **Evelyn, K. A.**, and **Malloy, H. T.**: J. Biol. Chem., **126**, 655, 1938. (11.) **Fildes, P.**: Brit. J. Exp. Path., **10**, 151, 197, 1929. (12.) **Fox, C. L., Jr.**, and **Cline, J. E.**: J. Clin. Invest., **19**, 123, 1940. (13.) **Fox, C. L., Jr.**, **Cline, J. E.**, and **Ottenberg, R.**: J. Pharm. and Exp. Ther., **66**, 99, 1939. (14.) **Fox, C. L., Jr.**, **German, B.**, and **Janeway, C. A.**: Proc. Soc. Exp. Biol. and Med., **40**, 184, 1939. (15.) **Gillespie, L. F.**: Soil Sci., **9**, 199, 1920. (16.) **Hardy, A. C.**: J. Ophth. Soc. Am., **28**, 360, 1938. (17.) **Harris, J. S.**: J. Clin. Invest., **18**, 521, 1939. (18.) **Harris, J. S.**, and **Michel, H. O.**: Ibid., p. 507. (19.) **Hartmann, A. F.**, **Perley, A. M.**, and **Barnett, H. L.**: Ibid., **17**, 699, 1938. (20.) **Hellerman, L.**, **Perkins, M. E.**, and **Clark, W. M.**: Proc. Nat. Acad. Sci., **19**, 855, 1933. (21.) **Kligler, I. F.**, and **Guggenheim, K.**: J. Bact., **35**, 141, 1938. (22.) **Lockwood, J. S.**, **Coburn, A. F.**, and **Stokinger, H. E.**: J. Am. Med. Assn., **111**, 2259, 1938. (23.) **Marshall, E. K.**: J. Biol. Chem., **122**, 263, 1937. (24.) **Mayer, R. L.**: Bull. de l'Acad. de méd., **117**, 727, 1938. (25.) **Ottenberg, R.**, and **Fox, C. L., Jr.**: Proc. Soc. Exp. Biol. and Med., **38**, 479, 1938. (26.) **Paton, J. P. J.**, and **Eaton, J. C.**: Lancet, **1**, 1159, 1369, 1937. (27.) **Rosenthal, S. M.**: J. Am. Med. Assn., **113**, 1710, 1939. (28.) **Schmelkes, F. C.**: Am. J. Pub. Health, **23**, 269, 1933. (29.) **Shwachman, H.**, **Hellerman, L.**, and **Cohen, B.**: J. Biol. Chem., **107**, 257, 1934. (30.) **Swift, H. F.**, **Lancefield, R. C.**, and **Goodner, K.**: Trans. Assn. Am. Phys., **1**, 217, 1935. (31.) **Warren, J.**, **Street, J. A.**, and **Stokinger, H. E.**: Proc. Soc. Exp. Biol. and Med., **40**, 208, 1939.

SCARLET FEVER THERAPY.

A COMPARISON OF CONVALESCENT SERUM AND SULPHANILAMIDE.

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THE object of this study is an attempt to compare the results following the use of human convalescent scarlet fever serum in the treatment of scarlet fever with those following the use of sulphanilamide. We have found, as have others, that when convalescent scarlet fever serum is given early in the disease in adequate amounts, there is an apparent decrease in the mortality rate, as well as a reduction in the complications. As a rule, all the symptoms improve, and there is a reduction in the length of time until the temperature reaches normal.[2]

Recently, the value of sulphanilamide in the treatment of scarlet fever has been studied by Wesselhoeft and Smith,[14] Peters and Harvard,[8] Schwentker and Waghelstein,[11] Sako, Dwan and Platou,[10] Hoyne and Bailey,[5] Hogarth,[4] Place,[9] and Strom.[12]

We have studied 300 hospital cases of scarlet fever, divided into groups of 100 each. The first group (A) received non-specific therapy and general care. The case types were ordinary in character and would be classified as mild. The cases in the second group (B) were mild or moderately ill and were given neoprontosil (Winthrop-Brand of Azosulfamide, Disodium 4-sulfamide-phenyl-2-azo-7-acetylamino-1-hydroxynaphthalene 3, 6-disulfonate). Patients in the third group (C) which were selected for convalescent serum therapy were moderately or severely ill. In each group the cases were divided into 5-year age periods up to the age of 20. All cases occurred during the same period of time, January, February, March and April of 1939. All were attended by the same professional personnel.

Method. Patients under 5 years of age were given 10 gr. of neoprontosil twice daily for 3 days. The following 4 days they were given 10 gr. once daily. From the 16th to the 23d day, 10 grains again were given daily. Those over 5 years of age were given 10 gr. 3 times daily for the first 3 days. The next 4 days 10 gr. twice a day. From the 16th to the 23d day, they were given 10 gr. twice daily. The medication was given 1 hour before meals, and was accompanied by soda bicarbonate. The second course of neoprontosil, beginning on the 16th day, was given to cover the third week complications which are apt to occur. The method of preparing and using convalescent scarlet fever serum has been described in a previous article.[3]

The control cases were admitted to the hospital somewhat later than were the cases in the other groups (see chart). In the serum-treated cases the temperature reached normal in a shorter length of time (1.7 days) than in the control (2.8 days).

TABLE 1.—COMPARISON OF NEOPRONTOSIL AND CONVALESCENT SCARLET FEVER SERUM IN THE TREATMENT OF SCARLET FEVER.

Ages.	A. Control (mild).						B. Serum (mod. and severe).						C. Neoprontosil (mod.).					
	0–5.	5–10.	10–15.	15–20.	20.	T.	0–5.	5–10.	10–15.	15–20.	20.	T.	0–5.	5–10.	10–15.	15–20.	20.	T.
Number of cases	18	56	18	3	5	100	7	32	15	14	32	100	12	41	17	6	24	100
Mean day of disease on admission	3	4	3.7	3.3	5.5	3.9	2	4.6	3	3	3	3.1	2.8	2.9	2.2	6	2.6	3.3
Mean duration of pyrexia after admission	3.3	2.5	3	1.6	1.2	2.3	2.5	2	1.2	1.1	1.5	1.7	3.8	4.5	2.9	2.3	3	3.3
Cervical adenitis	6	9	3	..	..	18	1	5	2	..	..	8	4	6	..	1	3	14
Otitis media	4	5	3	..	..	12	2	8	1	..	..	11	..	5	1	1	1	8
Peritonsillar abscess	..	1	..	..	..	1	..	..	1	..	..	1	..	..	..	..	1	1
"Arthritis" (synovitis)	..	..	..	..	..	..	..	1	..	2	1	4	..	1	2	1	2	6
Nephritis	..	2	..	..	..	2	..	..	..	1	..	1	..	2	..	..	..	2
Cellulitis or extremity infections	1	4	..	..	..	5	1	2	..	..	1	4						
Recrudescence	..	1	..	..	..	1	..	..	..	..	..	..	..	1	..	..	1	2
Cases having 1 or more comp. or recrudescence	8	22	3	..	..	33	2	16	4	2	2	26	4	15	3	3	7	32

It took longer for the patients' temperature to reach normal in the neoprontosil cases (3.3 days). A large number of cases between the ages of 5 and 10 occurred in each group. Cervical adenitis occurred 18 times in the control group, 8 times in the serum-treated group, and 14 times in the neoprontosil group. Otitis media occurred 12 times in the control group, 11 times in the serum group, and 8 times in the neoprontosil group. Peritonsillar abscess developed in 1 case of each group. Nephritis occurred once in the serum group, and was found in 2 cases in each of the other two groups. Extremity infections (onychia and paronychia) or cellulitis developed in 5 of the controls and in 4 of the serum group. Arthritis (small bone synovitis) occurring in the first 10 days of the disease was found 4 times in the serum group and 6 times in the neoprontosil group. A recrudescence of the disease was noted in 2 cases of the neoprontosil group and 1 of the control group. The number of cases having complications (recrudescence included) were 26 in the serum-treated group, 32 in the neoprontosil group, and 33 in the control group.

There was noted an appreciable effect on the toxic phase of the disease following the use of convalescent serum. Although these cases were admitted to the hospital earlier in the course of their disease, it will be noticed that there was an earlier disappearance of fever. Amelioration of throat symptoms, and a sense of well-being followed shortly after the use of the serum. Such phenomena were not noted after the neoprontosil or in the control group.

A condition resembling the toxic phase of the disease can be produced through the use of scarlet fever toxin (immunization) in which no bacteria are involved. Neoprontosil, in our experience, has not improved this condition.

McIntosh and Whitby[7] have pointed to the time lag before the drug becomes effective *in vivo* or *vitro* and the tendency to primary stimulation of bacterial growth. This "lag" in action is responsible for the failure of the drug to check the initial local multiplication and invasion of organisms. This lagging period may be sufficiently long to endanger the lives of patients. We have observed 6 instances in which it was thought advisable to withdraw neoprontosil and substitute serum.

Case Abstracts. The following 2 cases illustrate this point: CASE 1.—On April 17, 1939, Miss A. L., aged 23, developed a severe angina. Three days later a punctiform rash was noted over the entire body and extremities, but was most marked in the folds of the body. A septic fever curve was present. Sulphanilamide (180 gr. daily) had been given for 5 days when she was seen by one of us (M. F.). The patient was comatose and showed evidence of marked dehydration, respiratory difficulty and cyanosis. The temperature was 105°, the pulse rate was 140, the respiratory rate 38. She also presented an extremely congested throat, strawberry tongue, and scarlatiniform rash.

Convalescent scarlet fever serum (40 cc.) was given, followed later by 50 cc. The temperature dropped 4° within 24 hours. On the 3d hospital day, the patient was rational and able to eat her meals, but complained of pain in the right side of her chest. Examination presented evidence of lobar pneumonia, which was treated with sulphapyridine. On the 6th day of the lobar pneumonia, a bloody membranous cast of the trachea was expectorated and following this an uneventful hospital course ensued.

CASE 2.—R. M., aged 11, was admitted to the South View Hospital on February 27, 1939. Examination revealed a well-developed and well-nourished white male child, acutely ill, having a temperature of 103.6°, pulse 140, and respiratory rate 20. He presented marked circumoral pallor, injected pharynx and soft palate with a strawberry tongue and a fine scarlatiniform rash over the entire body. Pastia's sign was present.

The patient was given 10 gr. of neoprontosil 3 times daily, but on the 2d day of his hospital stay, the patient still had a septic fever curve and was delirious. It was thought best to discontinue the neoprontosil and give convalescent scarlet fever serum (40 cc.). This caused the patient's temperature to level off rapidly. There was marked clinical improvement and an uneventful convalescence followed.

Colebrook and Kenny,[1] and Long and Bliss[6] found that prontosil had little effect upon infections caused by the hemolytic streptococci of low mouse virulence. Although most of our cases were of moderate severity, we have seen severe early cases not notably improved after massive doses.

The total number of complications was less in the severe cases treated by convalescent serum than either of the other groups consisting of mild and moderate cases. Otitis media occurred less frequently in the neoprontosil group which may have been due to the drug or the milder type of this disease in these cases. A study of a larger number of cases is to be encouraged.[13] No cases of cellulitis or extremity infections occurred after the use of neoprontosil.

We feel, as a result of the above study and from other clinical experiences, that neoprontosil as well as convalescent serum has a place in the treatment of scarlet fever. However, it is not for the toxic phase or type of disease. Four cases of hemolytic blood stream infections occurring in scarlet fever have received the drug and have recovered. Otitis media and mastoiditis appear to have been helped by its administration. Two cases of hemolytic streptococcus meningitis following scarlet fever have been treated successfully by neoprontosil at South View Hospital. We have also noted improvement after its use in deep-seated recesses of infection. Surgical drainage necessarily complements the drug action.

Conclusion. Neoprontosil seems to have less effect on the initial toxicity and pyrexia of scarlet fever than does convalescent scarlet fever serum, though both have been found useful in the treatment of this disease.

REFERENCES.

(1.) **Colebrook, L.**, and **Kenny, M.**: Lancet, **1**, 1279, 1936. (2.) **Fox, M.**, and **Hardgrove, M.**: Arch. Int. Med., **60**, 494, 1937. (3.) **Hardgrove, M.**: Minnesota Med., **18**, 541, 1935. (4.) **Hogarth, J. C.**: Brit. Med. J., **2**, 1160, 1937. (5.) **Hoyne, A. L.**, and **Bailey, J. H.**: Arch. Pediat., **54**, 731, 1937. (6.) **Long, P. H.**, and **Bliss, E. A.**: J. Am. Med. Assn., **108**, 32, 1937. (7.) **McIntosh, J.**, and **Whitby, L. E. H.**: Lancet, **1**, 431, 1939. (8.) **Peters, B. A.**, and **Harvard, R. V.**: Ibid., **1**, 1273, 1937. (9.) **Place, E. H.**: New England J. Med., **219**, 571, 1938. (10.) **Sako, W.**, **Dwan, P. F.**, and **Platou, E. S.**: J. Am. Med. Assn., **111**, 995, 1938. (11.) **Schwentker, F. F.**, and **Waghelstein, J.**: Baltimore Health News, **15**, 41, 1938. (12.) **Strom, J.**: Acta Paediat., **28**, 333, 1939. (13.) **Wesselhoeft, C.**: Ann. Int. Med., **12**, 1473, 1939. (14.) **Wesselhoeft, C.**, and **Smith, E. D.**: New England J. Med., **219**, 947, 1938.

LIMITATIONS OF THE USE OF DIGITALIS FOR AMBULATORY PATIENTS WITH AURICULAR FIBRILLATION.*

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It is well recognized clinically that patients with auricular fibrillation who have little or no evidence of heart failure complain of pal-

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pitation, a feeling of discomfort and heart consciousness after exercise or emotional strain and rapid heart rate, even when their ventricular rates at rest may be normal or only slightly elevated. It has been claimed that if adequate doses of digitalis are given to patients with auricular fibrillation, the marked increase in the rate of the ventricles can be prevented (Mackenzie[11]). However, Blumgart[1] as a result of his experiments on ambulatory patients, concluded that digitalis slowed the resting ventricular rate in auricular fibrillation, but failed to protect the ventricles from the exaggerated response to exercise. The results of Boas[2] and Levy and Boas[8] are in accord with Blumgart's. Boas[2] and Boas and Goldschmidt[3] have suggested that patients with auricular fibrillation can be classed into (*a*) high-strung, nervous individuals with labile ventricular rates and (*b*) calm and phlegmatic individuals with stable ventricular rates. The latter group are readily kept under control by digitalis, but the former still exhibit exaggerated ventricular responses to exercise and emotional upsets even after thorough digitalization.

The apparent discrepancy between Mackenzie's experience and those of Blumgart and of Boas *et al.* suggested to us the need of reinvestigating this subject more systematically. Eight coöperative patients with auricular fibrillation from the Mandel Clinic were selected for intensive study. In 4 the etiology of the auricular fibrillation was chronic rheumatic heart disease, in 3 it was coronary sclerosis and in 1 it was a combination of the two. All of the patients were ambulatory.

Method. The patients were told to continue their habitual régime, and the digitalis medication was controlled. The exercise test employed was standardized for each patient by determining the amount of exercise the patient could tolerate on the Master stairs 3 weeks after digitalis had been stopped. The rate of exercise was the pace set at this time by the patient. The duration of exercise and the number of trips (of 5 steps) was measured. The exercise was terminated when the patient felt uncomfortable either because of palpitation, fatigue or shortness of breath. The same amount and rate of exercise were then used in all subsequent tests on the patient. Radial pulse and ventricular apex rates were determined simultaneously for 30 seconds in each test, (*a*) just before the exercise was begun, (*b*) 30 seconds after the exercise was over and every minute thereafter for at least 9 minutes. Before each exercise period the patient was allowed to rest in the sitting position for 15 minutes or more until the basal control rates were stabilized as checked by three consecutive readings. Only one exercise test was performed at each clinic visit. The effect of digitalis was then determined by repeating the same exercise at various stages of digitalization. In most of these patients the effect of digitalis was studied by repeating the control and digitalization periods several times.

Results. The results can best be presented by giving typical curves in 4 of the patients representative of several similar curves obtained on these and the other 4 cases.

Clinical Notes. Case 1.—R. C., a white male, aged 35, had rheumatic heart disease with mitral stenosis and insufficiency and aortic insufficiency.

His first attack had occurred 13 years previously, and he had been known to have auricular fibrillation for at least 4 years. At the time of examination the patient had had no digitalis for at least 6 weeks. He complained of some shortness of breath on slight exertion, attacks of palpitation and a feeling of general weakness, but there were no signs of cardiac failure on physical examination. His basal exercise consisted of 12 trips on the Master stairs in 68 seconds. The acceleration in ventricular rate following the exercise and the augmentation of the pulse deficit are clearly shown (Fig. 1, Records A). After the patient had received digitalis gr. iii daily for 1 week and gr. iss daily for 2 weeks, he showed not only a slower basal ventricular rate and practically absent basal pulse deficit but also a smaller ventricular acceleration and practically no pulse deficit (Fig. 1, Records B). No clinical or

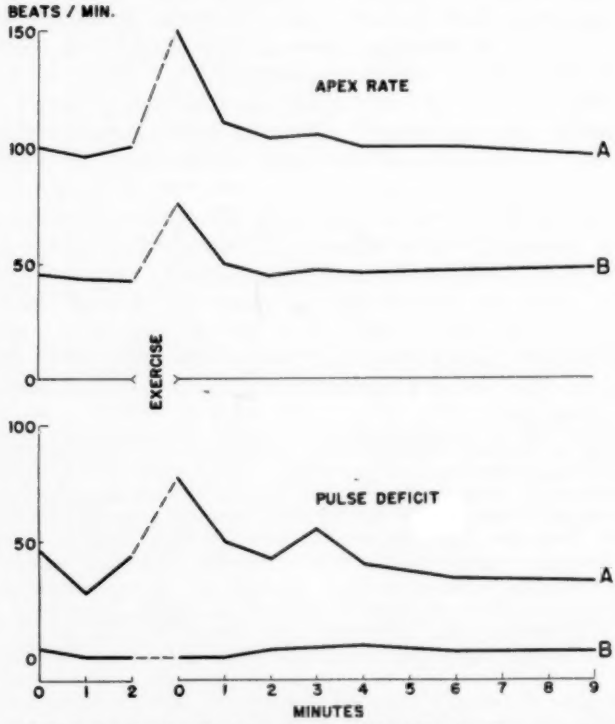

FIG. 1.—Effect of a standardized exercise on Patient R. C. Upper curves average apical ventricular rates; lower curves, pulse deficits. Exercise period is indicated by gaps in upper zero line. Discussed in text.

electrocardiographic evidences of digitalis intoxication were evident at this time and the patient stated that his shortness of breath, palpitation and weakness had disappeared. Digitalis had apparently not only slowed his basal rate but had lessened the effect of the standard exercise on his ventricular rate and the number of ineffective beats.

CASE 2.—A similar result was obtained on a second patient, A. S., a white male of 44 years, with rheumatic heart disease, mitral insufficiency and auricular fibrillation who had known that he had "heart trouble" for 7 years. At the time of examination the patient had stopped digitalis for

6 weeks. He complained of general weakness and shortness of breath even at rest. He appeared to be slightly cyanotic and had râles in both lung bases, a tender liver and slight ankle edema. His exercise at this time was 12 trips in 70 seconds (Fig. 2, Records A). Three weeks later after digitalization (20 gr. were given in the first 4 days followed by gr. iss daily), the signs and symptoms of cardiac failure had disappeared and there was no evidence of digitalis intoxication. The exercise test at this time gave results in all details exactly as in the preceding case (Fig. 2, Records B). The maintenance dose of digitalis was then reduced to gr. i every 2 days and 3 weeks later the exercise was repeated (Fig. 2, Records C). It will be seen that the

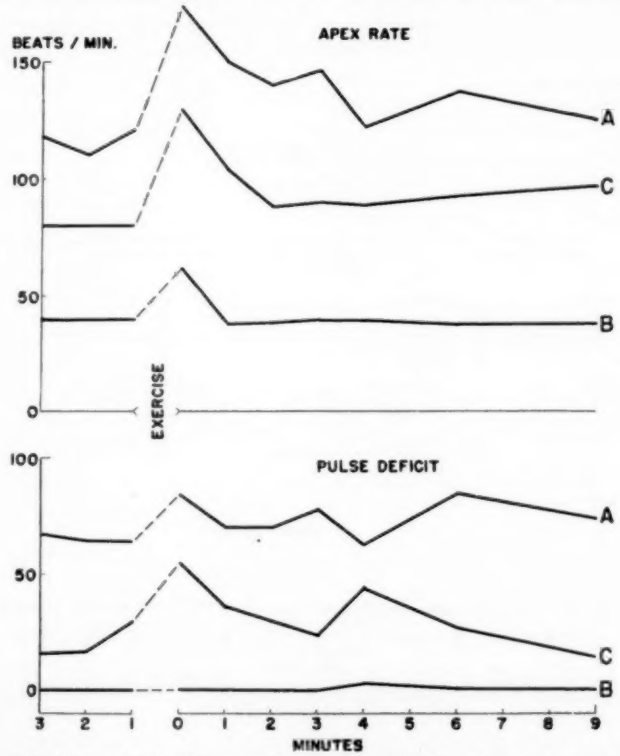

FIG. 2.—Effect of a standardized exercise on Patient A. S. Constructed as in Fig. 1. Discussed in text.

curves are intermediate between A and B and represent partial digitalization. Although the patient did not present any evidence of heart failure at this time, he stated of his own accord that he felt better while taking the larger doses of digitalis. Apparently, complete digitalization was necessary in this patient to minimize the effects of exercise on heart rate and the number of ineffective beats.

When the ventricular rate is around 60, under the basal conditions, digitalis has little or no effects on the action of exercise (Fig. 3). Curves A were taken when the patient J. K. had been off digitalis for 3 weeks.

CASE 3.—J. K., a white male of 58, had had evidence of mild heart failure for 5 years. His chief complaints were dyspnea after walking a block, orthopnea and occasional attacks of precordial pain. There was evidence of left ventricular enlargement, and slight edema. Blood pressure was 140/85. Extrasystoles of ventricular origin and auricular fibrillation were confirmed by the electrocardiogram. Despite the presence of mild heart failure, the effect of exercise (8 trips in 65 seconds), is similar to that in the fully digitalized states of the other patients. The patient was put on digitalis gr. iii daily for 4 weeks and then the same exercise was repeated. The results are shown in Records B, which are similar to A except that the basal apex rate is at a slightly lower level. The patient at the time of the second test had noticed no change in his condition while on the digitalis and his physical findings were also unchanged at this time.

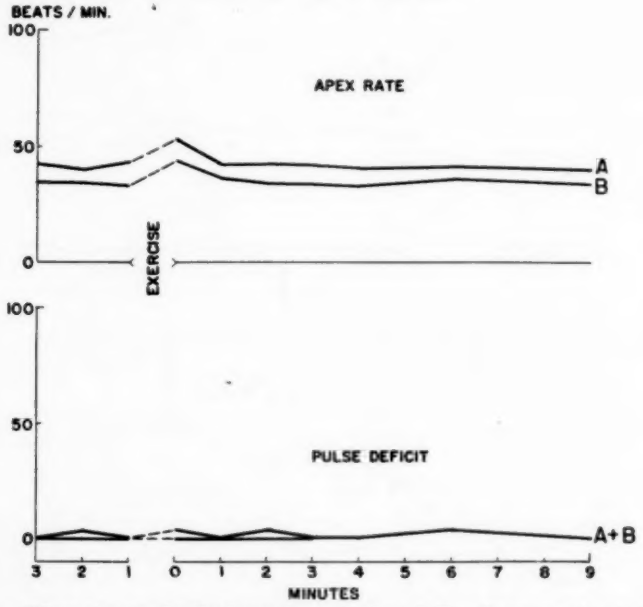

FIG. 3.—Effect of a standardized exercise on Patient J. K. Constructed as in Fig. 1. Discussed in text.

The lack of effect of digitalis on the exercise test was characteristic of all 4 cases of auricular fibrillation on a coronary sclerosis basis having a slow basal ventricular rate, and suggests that when the A–V conduction is noticeably impaired before medication, digitalis exerts little or no further action.

When digitalis was seemingly without effect in one patient, the usual digitalis action was readily obtained when this patient was placed in the hospital and given similar doses of digitalis (Fig. 4).

CASE 4.—A. F., a white woman of 51, had rheumatic heart disease and mitral stenosis occurring with her first attack of rheumatic fever 34 years before. She had had her first attacks of paroxysmal auricular fibrillation 2 years previously. When this patient had been without digitalis for some time,

the exercise which consisted of 11 trips in 90 seconds, produced a moderate acceleration and no added pulse deficit (Fig. 4, Records A). At the time of the test the patient's sole complaint was a feeling of weakness, but there were no signs of failure on physical examination. After the control exercise test, the patient was put on digitalis gr. iii b.i.d. for 1 week, gr. iii daily for a second week and then gr. iss daily for a third week, at which time the exercise test was repeated. The curves obtained were similar to the control except that the apex rate was at a slightly lower level. Following this, digitalis

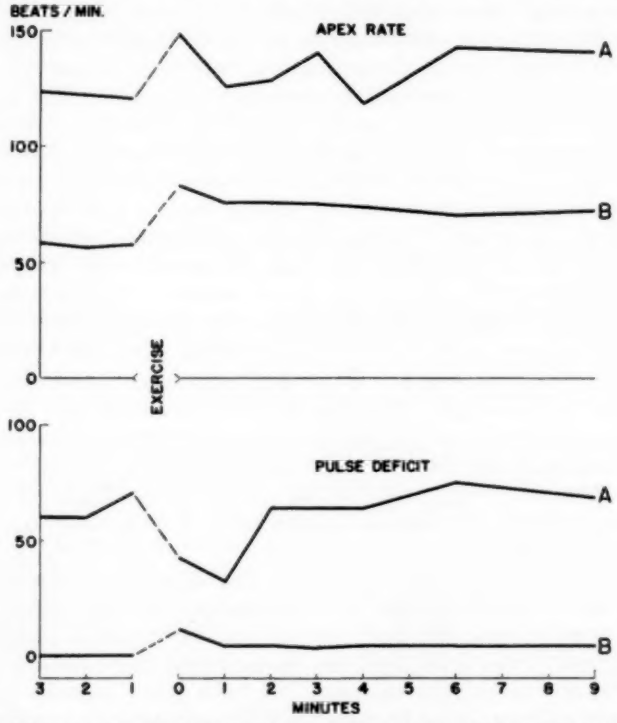

FIG. 4.—Effect of a standardized exercise on Patient A. F. Constructed as in Fig. 1. Discussed in text.

dosage was increased to gr. iii daily and at the end of 3 weeks an exercise test again gave results similar to the control. After 3 more weeks at a dosage of gr. ivss daily the exercise test again gave results differing little from those of Records A. It was therefore decided to place the patient on absolute bed rest in the hospital. This procedure without change in the dose of digitalis, rapidly led to a slowing in ventricular rate, so that within a week the dose of digitalis could be gradually reduced from gr. ivss to gr. iss daily. The exercise test was taken at the end of the week, but the duration of exercise was 5 instead of 1½ minutes (Fig. 4, Curves B). It will be seen that despite the greater amount of exercise, the exercise produced less change in ventricular rate than before digitalis was administered. At this time she stated that she could have kept up the exercise indefinitely.

Discussion. Our results suggest that the lack of effect reported by Blumgart and Boas *et al.* in certain cases of auricular fibrillation

were due to incomplete digitalization on the one hand, or to the presence of a slow ventricular rate and small pulse deficit in the absence of digitalis. Inadequate dosage of digitalis and a slow ventricular rate in the absence of digitalis appear to be the two chief circumstances which prevent the effective action of digitalis during exercise and presumably during emotional upsets, but the last case we reported shows that in some instances protracted rest is also necessary before this digitalis effect can be induced.

It seems to us that this sedative effect of digitalis in the presence of physical and emotional exertion is an important factor contributing to the clinical improvement noted in such cases. The ambulatory cardiac patient is constantly subject to physical and emotional exertion as part of his everyday existence, and therefore is not under basal conditions most of the time. If these exertions are accompanied by a great acceleration of ventricular rate with an exaggeration of the pulse deficit in the absence of digitalis, then the work of the heart will be done less efficiently than when the rate is kept slow. Each contraction of the heart requires the expenditure of energy whether the beat is effective or not. In rapid irregular heart action the energy cost of the work is out of proportion to the amount of blood flow maintained.[7] When the heart is in a poor state or in incipient failure, rapid irregular heart action will lead, by itself, to an aggravation of the failure. Anything which can prevent this wastefulness during stress by preventing excessive acceleration of the rate and exaggeration of the pulse deficit will therefore lead to improvement of the patient's condition. This is one of the things digitalis can do.

Our experience, therefore, suggests that digitalis in maintenance doses not only reduces the basal ventricular rate and pulse deficit at basal conditions, but also can prevent the excessive acceleration of the ventricular rate and the exaggerated pulse deficit during physical and emotional exertion. In both ways digitalis protects the heart and permits it to meet the daily strains which ambulatory patients are subject to with less ill effect. While tachycardia is a means by which the heart can maintain an adequate circulation when its stroke output is reduced (Luten[10], Wiggers[14]), it is not an efficient way. Tachycardia itself can lead to heart failure when it is excessive or when the heart action is very irregular (*cf.* Gross[7]).

The effectiveness of a given dose of digitalis will depend to some extent upon the natural balance of the action of the vagi and sympathetic nerves, and upon the adrenalin content of the blood, since these influence A–V conduction definitely (Carlen and Katz[4]), and these factors alter to a varying extent in different subjects.

Digitalis depresses A–V conduction (*cf.* Lewis,[9] Cushny,[5] and Weese[13]), in part by a direct action and in part through stimulation of the vagi. Gold *et al.*[6] have shown that the vagus action predominates with smaller doses and the direct action with larger doses of

digitalis. Obviously when the A–V conduction is naturally depressed as in the slow ventricular rates of auricular fibrillation on a coronary sclerosis basis, digitalis can do little more in this regard. In these cases Nature has done what digitalis does in patients with auricular fibrillation and rapid ventricular rates (Mackenzie,[11] and Robinson[12]).

This study suggests a method by which the adequacy of digitalis medication in a patient with auricular fibrillation may be tested. It would appear that the aim should be to give that amount of digitalis which not only keeps the basal rate slow but minimizes the acceleration of the ventricular rate on standardized exertion.

Summary. Digitalis, when used in large therapeutic doses was found to lessen the ventricular acceleration which occurs following a standardized exercise test in ambulatory patients with auricular fibrillation. It also decreased the pulse deficit at the same time. It was not effective in patients who already had a slow ventricular rate. Protracted rest, as well as large doses, may be required to produce slowing.

The tendency to prevent acceleration during exertion and emotional stress represents one of the modes of clinical benefit derived from digitalization.

REFERENCES.

(1.) **Blumgart, H.**: Heart, **11**, 49, 1924. (2.) **Boas, E. P.**: Am. Heart J., **4**, 499, 1929. (3.) **Boas, E. P.**, and **Goldschmidt, E. F.**: The Heart Rate, Springfield, Ill., Charles C Thomas, 1932. (4.) **Carlen, S. A.**, and **Katz, L. N.**: Am. J. Physiol., **127**, 272, 1939. (5.) **Cushny, A. R.**: Digitalis and Its Allies, London, Longman, Green & Co., 1925. (6.) **Gold, H., Kwit, N. T., Otto, H.**, and **Fox, T.**: J. Clin. Invest., **18**, 429, 1939. (7.) **Gross, H.**, and **Sparks, C.**: Am. Heart J., **14**, 160, 1937. (8.) **Levy, H.**, and **Boas, E. P.**: Ibid., **15**, 643, 1938. (9.) **Lewis, T.**: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Shaw, 1925. (10.) **Luten, D.**: The Clinical Use of Digitalis, Springfield, Ill., Charles C Thomas, 1936. (11.) **Mackenzie, J.**: Diseases of the Heart, 4th ed., London, Oxford University Press, 1925. (12.) **Robinson, G. C.**: Medicine, **1**, 1, 1922. (13.) **Weese, H.**: Digitalis, Leipzig, Georg Thieme, 1936. (14.) **Wiggers, C. J.**: J. Am. Med. Assn., **96**, 603, 1931.

CIRCULATION TIME (MAGNESIUM SULPHATE METHOD) IN THE DIAGNOSIS OF PERIPHERAL VASCULAR DISEASE.*†

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Little consideration has been given in the past to the circulation time within any part of the vascular circuit which included within it, to a large extent, the arterial supply of the extremities.[4,28,29,35,43,45,47] Yet, it would seem plausible to suppose that

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individuals with vascular disease of the limbs might display circulation times to the tips of the extremities different from that of normals. Should this actually be true then the determination of the circulation time to the tips of the extremities would find application as a diagnostic test of the presence or absence of peripheral vascular disease. In order to evaluate that supposition, this study was undertaken to determine what might be the normal circulation time from the arms to the tips of the extremities and to compare these times with similar times obtained in known cases of peripheral vascular disease.

Selection of Patients. Two hundred "normal" individuals were selected from the ward and clinics of the hospital and from volunteers, all of whom were free of clinical peripheral vascular disease. Excluded were cases with cardiovascular disease, pulmonary disease, fever, anemia or other diseases of the blood or metabolism. Upon these were performed 405 complete tests, or, counting each extremity, 1593 tests.

Twenty-one cases of peripheral vascular disease were chosen from among the attendants at the Vascular Clinic and hospital patients admitted because of peripheral vascular disease. All of these patients were free at all times of cardiac decompensation. Upon these were performed 83 complete tests or, counting each extremity, 332 tests.

Agent Used. Blumgart and Yens[8] have postulated the essential requirements that any substance must fulfill in order to be suitable for use in the determination of circulation time. Magnesium sulphate, originally suggested by Zwillinger,[51] has been successfully used by several investigators in determining circulation time.[6,42,47] In this study magnesium sulphate was selected as the agent after analyzing it in the light of the postulates of Blumgart and Yens.

The substance when given intravenously was non-toxic and harmless. The end reaction was sharp and sudden. In a group of 43 normal individuals the net effect of the magnesium sulphate was negligibly to reduce both phases of the blood pressure (1.5 to 4.0 mm. of Hg) and negligibly to reduce the pulse rate (1 per minute). Rapid repetition of the test on each of approximately 100 individuals permitted the conclusion that magnesium sulphate could be reinjected into the same individual at intervals as short as 5 minutes without materially altering the accuracy of the circulation times obtained. No thromboses and no sloughs were encountered in over 500 injections although paravenous infiltration did produce pain and tenderness for a short period. The salt is easily obtained and its preparation for suitable intravenous injection is so simple that the cost is practically *nil.*

It was felt, therefore, that magnesium sulphate met all the requirements of a substance suitable for use in the determination of circulation time with the sole exception of the requirement demanding no coöperation on the part of the patient.

Method. *Solution.* Ten per cent C.P. magnesium sulphate solution in distilled water stored in ampoule vials and autoclaved.

Dosage. 5 cc. of the 10% magnesium sulphate given intravenously.

Rate of Injection. Every effort is made to secure as rapid an introduction of the solution into the vein as possible. By experimentation with various sized syringes and needles it was found that the most rapid injection time followed the use of a 10 cc. syringe and a No. 18 gauge needle (0.4 to 0.8 sec.).

Technique. All patients were tested under as basal a condition as the clinical circumstances permitted. The individual, at least 3½ to 4 hours

having elapsed since the last meal, was placed at bed rest in the dorsal decubitus for a period not less than 10 to 15 minutes. Most patients were already at bed rest when approached for the performance of the test. Those who were ambulatory, and in particular those who were in attendance at the various out-patient clinics, were first permitted to sit about quietly for some time before the additional bed rest, just preceding the injection. A detailed explanation was made to every patient as to the nature of the procedure about to be performed, the sensations to be expected, the manner in which the end points were to be announced and the general import of the test. By these means an attempt was made to allay anxiety and nervousness, obviate apprehension and secure the intelligent coöperation of the individual. The arm was supported upon a pillow on a level approximately with the entrance of the venæ cavæ into the right auricle. Either arm was used and in many individuals repeated tests were made in alternate arms. Following the proper preparation of the antecubital space, the needle was engaged into the most accessible antecubital vein and the tourniquet was then removed. A few moments were permitted to elapse so as to allow the patient to regain his composure. During this interval there was again described the warm sensation that would appear in the back of the tongue and sweep down the body to the tips of the extremities. An assistant held the stopwatch while the count "1, 2, 3," was loudly made. On the "3" the watch was started simultaneously with a rapid injection of the material. At the first perception of warmth at the tongue and at the tips of each extremity the patient cried out loudly "tongue," "right hand," "left hand," "left foot," "right foot," "both hands," or "both feet," as the case might be. Two minutes were allowed for sensations to appear at all the end points. Any end point not registering a sensation in that period of time was labeled as a "blank." Should that same extremity yield no sensation on 2 or more repeated tests, the tests were held to be "persistent blanks."

Results. There is a clear prolongation of the average circulation time from the arm to the tips of the extremities in the peripheral vascular disease group as compared with the normals (Table 1). But, there is apparent a wide overlapping of the ranges of the normal and of the peripheral vascular disease groups (Table 1) which would tend to invalidate any conclusive comparisons of average times.

TABLE 1.—ARM-TO-HAND AND ARM-TO-FOOT CIRCULATION TIMES.

	No. of individuals		No. of tests.		Range.		Average time (sec.).		Average deviation.	
	N.	PVD.	N.	PVD.	N.	PVD.	N.	PVD.	N.	PVD.
Arm-to-rt. hand	200	21	405	83	6.0–61.3	12.2–54.0	19.3	25.7	±5.2	± 6.3
Arm-to-lt. hand	200	21	401	83	6.0–52.2	14.1–66.4	19.1	24.5	±4.9	± 6.3
Arm-to-rt. foot	199	21	392	83	7.4–50.1	18.0–70.1 (117.2)	23.8	35.7	±6.0	±10.4
Arm-to-lt. foot	200	21	395	83	8.2–56.2	18.0–75.0	24.4	36.1	±6.7	±10.9

In the peripheral vascular disease group as compared with the normals, more than twice as many individuals and almost three times as many tests yielded "blanks" at some time or other, while more than three times as many individuals and almost twice as

many tests yielded "persistent blanks" (Table 2). This is more striking when one considers that over two-thirds of all individuals with peripheral vascular disease display "blank" reactions at some time or other.

TABLE 2.—DISTRIBUTION OF BLANK TESTS—ALL EXTREMITIES.

	No. of ind. tested.	No. of tests performed.	Blanks.				Persistent blanks.			
			Ind. rep.	Total ind., %.	No. tests.	Total tests, %.	Ind. rep.	Total ind., %.	No. tests.	Total tests, %.
Normals .	200	1593	64	32.0	211	13.3	15	7.5	84	5.3
Entire group PVD. .	21	332	14	66.7	112	33.8	5	23.8	33	9.9

It seems that a "blank" reaction might be in part a manifestation of a circulation time so prolonged that no terminal sensation was manifest. To support this hypothesis we were able to demonstrate longer average circulation times in those individuals who never experienced "blanks," as compared to those who did experience "blanks" at some time or other. Hence, were it possible to attribute a numerical value to each "blank," it would appear that the average time obtained in the peripheral vascular disease group would far exceed that of the normals and the average ranges would become so far separated from each other that there would be no longer the overlapping observed. Furthermore, it was noted throughout that the greater the number of tests performed on any one individual, the less the likelihood of obtaining "persistent blanks" except in those with peripheral vascular disease.

With the thought in mind that the longer circulation times in the peripheral vascular disease class may be in some way related to the older age groupings of the peripheral vascular disease patients, a comparison was made in the normal group (where the sample was sufficiently large) of the average circulation times in the various age classes. Both the arm-to-tongue and the arm-to-extremity times showed a definite trend toward the prolongation of circulation time with advancing age.

An attempt was made to classify the 21 patients with known peripheral vascular disease on the basis of the severity of their disease into "severe," "moderate," and "mild" groups. No single definitive measure was used to separate these, but rather a combined clinico-laboratory evaluation. A comparison of the average times in these groups revealed a definite and distinct prolongation of the circulation time parallel with the degree of peripheral vascular impairment.

In like manner, it appeared that the average circulation time from the arms to the tips of the extremities was longer to the more involved extremity than it was to the opposite one

Comment. A striking and important fact that was evident throughout this study was the great variation in circulation times obtained both in the same and between different individuals. It would seem that there are either inherent in the method or linked with the long circulatory pathway several influences that tend to induce varying results even in the same individual.

First, there is an inadequacy in the method. The use of magnesium sulphate renders the determination of the circulation time purely a subjective one. On that account, "circulation time" becomes really "circulation time" plus "reaction time" on the part of the patient as well as on the part of the observer.

Second, there are present before and during the performance of the test many physiologic factors which produce marked variations in the blood flow in the extremities. These include: 1, spontaneous variation in vasomotor tonus;[1] 2, varying environmental conditions;[1,13,15,17,19,21,24,36,37,38b] 3, traumatic stimuli;[1,13,18] 4, ingestion of food;[1,38a] 5, sleep;[1] 6, exercise;[16,38b] 7, sensory stimuli;[18,21,41] 8, pregnancy;[6,22] 9, age. Blumgart[7] concluded that the velocity of blood flow through the lungs showed no constant relationship to the age of the patient. Candel[12] likewise concluded that there was no correlation between age and circulation time. However, children have been shown to exhibit slightly more rapid circulation times than adults[3] and the results of our own studies would infer that the velocity of blood flow tends to diminish with advancing age.

Third, it has been adequately established that the velocity of blood flow varies with several pathologic states which may, in mild form, exist unrecognized in the individual being tested, such as anemia,[9] fever[30,32] and hyper- and hypometabolic states.[7,20,39]

An attempt was made in our material to eliminate or minimize these various influences through the selection of the subjects and the method of performance of the test as previously described. Yet, our success in so doing must, of necessity, have been variable and non-predictable. Because of this, it is apparent that a single determination of the circulation time from the arms to the tips of the extremities yields little information as to the average basal velocity of blood flow in the extremities of that individual.

The great preponderance of "blank" reactions in cases of peripheral vascular disease should be emphasized. It is extremely important, because of this, to appreciate that in the recognition of the presence of peripheral vascular disease from a study of the velocity of blood flow, the frequency and persistency of "blank" reactions is as much a determining finding as the actual circulation times obtained.

The explanation of why there should be longer circulation times and more "blank" reactions in cases of peripheral vascular disease affords interesting speculation. There are present in individuals with peripheral vascular disease several physico-anatomical changes

that would tend to retard the velocity of blood flow: These include: 1, Premature reduction in the head of pressure through overcoming the increased resistance encountered prior to the arteriolar-capillary junction. 2, Increased resistance to blood flow accruing from a combination of: (*a*) rigidity of the vessels; (*b*) encroachment on the lumen; (*c*) irregularity of the intima; (*d*) irregularity of the vessels. 3, Increase in the viscosity of the blood.[5,31,40,46,49] 4, Increase in cross-sectional area resulting from: (*a*) The development of collateral channels;[2,11,36,48,49,50a,b] (*b*) dilatation of vessels in territory deprived of blood;[18,36] (*c*) less intermission of capillary flow;[10,14,23,25,27,33,44] (*d*) loss of physiologic variability of the blood-vessels.[2,34] 5, Disorderly blood flow.[2,36,48,49,50a,b] 6, Dispersion of the test substance. 7, Possible higher threshold of stimulation of sensory end organs in areas with poor blood supply. 8, Possible concomitant cardiac inefficiency.

Patients with disease of their peripheral blood-vessels might well have concomitant disease of their coronary vessels and hence myocardial changes impairing the cardiac adequacy as a pump. To determine to what extent cardiac efficiency might affect the arm-to-hand and arm-to-foot circulation times, it was decided to evaluate the shorter arm-to-tongue circulation time in the same group. The latter is accepted as representing roughly the total cardiac circulation time, and, while not by any means conclusive, affords an isolated measure of the functional status of the heart. Accordingly, 340 tests were performed on 166 normal individuals and 74 tests were performed on the 21 individuals with peripheral vascular disease. Table 3 demonstrates a definite increase in the arm-to-tongue circulation time in the peripheral vascular disease group over that in the normals. Here, as in the arm-to-extremity times there is also overlapping in the average ranges, so that absolute and wide separation of the times are not possible.

TABLE 3.—ARM-TO-TONGUE CIRCULATION TIMES.

	No. of individuals.	No. of tests.	Range.	Average time (sec.).	Average deviation.	Blanks.	
						No.	Total tests, %.
Normals	166	340	4.0–20.2	10.4	±2.0	3	0.9
Peripheral vascular disease	21	74	8.0–26.3	13.5	±2.2	1	1.4

Conclusions. 1. By this method there seems to be some prolongation in circulation time in a *group* of patients with peripheral vascular disease as compared to normal subjects, and in *groups* of older subjects as compared to younger subjects.

2. There also seems to be an increase in the number of "blank" reactions in the same group of patients with peripheral vascular disease as compared to normal subjects.

3. *But*, individual variations and overlap are so great that this method cannot be recommended for testing the peripheral circulatory efficiency of a *given* patient.

Summary. 1. The arm-to-tongue and arm-to-extremity circulation times were determined upon 200 normal subjects and 21 patients with peripheral vascular disease through the intravenous injection of 5 cc. of 10% magnesium sulphate solution.

2. Individuals with peripheral vascular disease exhibited a tendency toward a longer circulation time and a definite increase in the number of "blank" and "persistent blank" reactions.

3. Wide variations in circulation times were obtained both in the normal and in the abnormal groups even within the same individual. The possible reasons for this were discussed.

4. The possible explanations for the prolonged circulation times and the greater number of "blank" reactions in peripheral vascular disease were discussed.

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REFERENCES.

(1.) **Abramson, D. I., Zazeela, H.,** and **Marrus, J.**: Am. Heart J., **17**, 206, 1939. (2.) **Allen, E. V.**: Arch. Int. Med., **57**, 601, 1936. (3.) **Averbuck, S. H.,** and **Friedman, W.**: Am. J. Dis. Child., **49**, 361, 1935. (4.) **Bartels, E. C.,** and **Powelson, M. H.**: Proc. Staff Meet. Mayo Clin., **4**, 217, 1929. (5.) **Bernheim, A. R.,** and **London, I. M.**: J. Am. Med. Assn., **108**, 2102, 1937. (6.) **Bernstein, M.,** and **Simpkins, S.**: Am. Heart J., **17**, 218, 1939. (7.) **Blumgart, H. L.**: Medicine, **10**, 1, 1930. (8.) **Blumgart, H. L.,** and **Yens, O. C.**: J. Clin. Invest., **4**, 1, 1927. (9.) **Blumgart, H. L., Gargill, S. L.,** and **Gilligan, D. R.**: Ibid., **9**, 679, 1931. (10.) **Bordley, J., III, Grow, M. H.,** and **Sherman, W. B.**: Bull. Johns Hopkins Hosp., **62**, 1, 1938. (11.) **Brown, G. E., Allen, E. V.,** and **Mahorner, H. R.**: Thrombo-Angiitis Obliterans, Mayo Clin. Monographs, Philadelphia, W. B. Saunders Company, 1928. (12.) **Candel, S.**: Ann. Int. Med., **12**, 236, 1938. (13.) **Capps, R. B.**: J. Clin. Invest., **15**, 229, 1936. (14.) **Carrier, E. B.**: Am. J. Physiol., **61**, 528, 1922. (15.) **Dail, C. W.,** and **Moore, F. B.**: Arch. Phys. Ther., **19**, 135, 1938. (16.) **Ellis, L. B.**: Am. J. Physiol., **101**, 494, 1932. (17.) **Freeman, N. E.**: Ibid., **113**, 384, 1935. (18.) **Freeman, N. E., Shaw, J. L.,** and **Snyder, J. C.**: J. Clin. Invest., **15**, 151, 1936. (19.) **Gibbon, J. H.,** and **Landis, E. M.**: Ibid., **11**, 1019, 1932. (20.) **Goldberg, S. J.**: Ann. Int. Med., **11**, 1818, 1938. (21.) **Grant, R. T.,** and **Pearson, R. S. B.**: Clin. Sci., **3**, 119, 1938. (22.) **Greenstein, N. M.,** and **Clahr, J.**: Am. J. Obst. and Gynec., **33**, 414, 1937. (23.) **Hagen, W.**: Ztschr. f. ges. exp. Med., **14**, 364, 1921. (24.) **Henderson, Y., Oughterson, A. W., Greenberg, L. A.,** and **Searly, C. P.**: Am. J. Physiol., **114**, 269, 1936.

(25.) **Hinselmann, H.**: Zentralbl. f. Gynäk., **45**, 7, 1921. (26.) **Hinselmann, H.,** and **Haupt**: Deutsch. med. Wchnschr., **47**, 590, 1921. (27.) **Hinselmann, H., Nettekoven, H.,** and **Silberbach, W.**: Ztschr. f. Geburtsh. u. Gynäk., **84**, 673, 1922. (28.) **Kahler, H.**: Wien. Arch. f. inn. Med., **19**, 1, 1929–1930. (29.) **Katz, G.**: München. med. Wchnschr., **79**, 2048, 1932. (30.) **Kissin, M.,** and **Bierman, W.**: Proc. Soc. Exp. Biol. and Med., **30**, 527, 1933. (31.) **Koga, G.**: Deutsch. Ztschr. f. Chir., **121**, 371, 1913. (32.) **Kopp, I.**: Am. Heart J., **11**, 475, 1936. (33.) **Krogh, A.**: (*a*) J. Physiol., **52**, 457, 1918–1919; (*b*) The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922. (34.) **Landis, E. M.**: Ann. Int.

Med., **10**, 290, 1936. (**35.**) **Leschke, E.**: München. med. Wchnschr., **2**, 2117, 1931. (**36.**) **Lewis, T.**: Vascular Disorders of the Limbs, New York, The Macmillan Company, 1936. (**37.**) **Lewis, T.**, and **Pickering, G. W.**: Heart, **16**, 33, 1931. (**38.**) **McCracken, E. C., Sheard, C.**, and **Essex, H. B.**: (*a*) Proc. Staff Meet. Mayo Clin., **10**, 548, 1935; (*b*) Ibid., p. 600. (**39.**) **Macy, J. W., Clarborne, T. S.**, and **Hurxthal, D. M.**: J. Clin. Invest., **15**, 37, 1936. (**40.**) **Mayesima, J.**: Mitt. a. d. Grenzgeb. d. Med. u. Chir., **24**, 413, 1911. (**41.**) **Molitor, H.**, and **Kniazuk, M.**: J. Pharm. and Exp. Ther., **57**, 6, 1936. (**42.**) **Neurath, O.**: Ztschr. f. klin. Med., **132**, 134, 1937. (**43.**) **Prusik, B. K.**: Casop. lek. cesh., **68**, 1713, 1929. (**44.**) **Richards, A. N.**, and **Schmidt, C. F.**: Am. J. Physiol., **71**, 178, 1924. (**45.**) **Robb, G. P.**, and **Steinberg, I.**: Am. J. Radiol., **41**, 1, 1938. (**46.**) **Samuels, S. S.**: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford Medical Publications, 1936. (**47.**) **Spier, L. C., Wright, I. S.**, and **Saylor, L.**: Am. Heart J., **12**, 511, 1936. (**48.**) **Stein, I. D.**: Ibid., **14**, 726, 1937. (**49.**) **Veal, J. R.**, and **McFetridge, E. M.**: J. Am. Med. Assn., **104**, 542, 1935; Ann. Surg., **101**, 766, 1935. (**50.**) **Yater, W. M.**: (*a*) Am. Heart J., **12**, 383, 1936; (*b*) Am. J. Med. Sci., **194**, 372, 1937. (**51.**) **Zwillinger L.**: Klin. Wchnschr., **14**, 1429, 1935.

THE CLINICAL SIGNIFICANCE OF BILATERAL EDEMA OF THE LOWER EXTREMITIES.

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The occurrence of edema of the lower extremities is such a commonplace phenomenon in medical practice, and has been so thoroughly studied, that it would at first thought seem unnecessary to write of its clinical significance. However, too frequently there have been brought to our attention cases with edema attributed to heart failure which when properly evaluated is clearly due to other conditions. Many patients are given digitalis for supposed congestive failure when their edema actually is due to varicose veins, nutritional factors, phlebitis, or other non-cardiac cause. A survey of several of the textbooks on diagnosis shows that too little emphasis is placed on the significance of varicose veins, posture and other simple factors in the production of edema. It was evident that a careful clinical study of a group of cases would be of value to determine the relative incidence of the causative factors in dependent edema.

With this in mind, we have recently collected from the Out-Patient Department of the Massachusetts General Hospital 100 unselected cases of bilateral edema of the lower extremities. Cases of uni-

lateral edema were not collected because they would obviously not be confused with edema due to congestive heart failure. Out-patients, coming because of varied complaints, mostly attended the general medical and surgical clinics. Such an out-patient series is thus comparable to the group of patients encountered in general medical practice. In addition, we collected 100 cases of bilateral edema of the legs from the medical and surgical wards.

The essential criterion in the selection of cases has been that the patients must show to us definite palpable edema of the feet, ankles or pretibial areas. The hospital ward group was for the most part made up of bed patients at the time of examination, while the out-patient group was ambulatory and examined in the morning at the time of admission after they had been up and about for several hours. They were not selected on the basis of history, routine physical examinations and laboratory studies; in some instances, special laboratory procedures were also done. The edema was classified as slight, moderate, or marked, *i. e.*, minimal pitting of ankles or pretibial regions (slight), more pronounced edema reaching to the mid-leg (moderate), or severe swelling up to and above the knees (marked). An attempt was made to determine carefully in each instance the various factors involved in the causation of the edema.

Analysis of Material. *The Out-Patient Department Group.* (See Table 1.) It is quite evident that the largest number of cases is that due to varicose veins with or without obesity. Of the 56 cases in which varicose veins were important factors, the edema was slight in 34, moderate in 20 and marked in only 2 cases. On the basis of our experience and that of others,[3,5] uncomplicated varicose veins very seldom, if ever, cause marked edema (of the 21 cases, 16 were of slight and 5 of moderate amount). Varicose veins complicated by incompetent communicating veins, thrombophlebitis of the femoral or iliac veins, poor nutrition, congestive failure, obesity, and so on, may be associated with more severe degrees of edema.

It will be noted that there were only 13 cases due to congestive heart failure, and an equal number due to obesity alone. Of the 3 cases attributed to nutritional deficiency states, 1 had a gastro-intestinal malignancy, and the other 2 were the result of dietary deficiencies. Lymphedema (due to chronic epidermophyton infection and to recurrent inflammatory processes of unknown origin) nephrosis, acute nephritis and cirrhosis of the liver were infrequent contributors to this group.

Of the remaining 6 cases in the miscellaneous group, 1 of rheumatoid arthritis had slight edema of obscure origin; in a cancer of the cervix with metastases to the liver, the edema most probably was due to circulatory obstruction; 1 had bilateral phlebitis of the femoral veins; 1 had myxedema; and there were 2 with no definite cause to be blamed for the edema. One of the last 2 cases had heart disease, but there was no evidence of heart failure, and digitalis

and other cardiac therapy were unsuccessful in relief of the edema; the other had edema for 10 or 12 years, during which time many studies were made but no cause for the edema found.

With regard to the symptoms in this group of cases, it was found that 71 complained of some degree of dyspnea (though only 22 had heart disease and only 13 of those had congestive failure). Among the 56 patients with varicose veins, 49 had dyspnea. This dyspnea

TABLE 1.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.
(Distribution of Cases Seen in the Massachusetts General Hospital Out-patient Department.)

		Varicose veins—obesity.						Renal.						
		Varicose veins without obesity.		Obesity without var. v's.	Obesity and varicose veins.		Heart failure.	Acute nephritis.	Nephrosis.	Nutritional.	Lymphedema.	Cirrhosis of liver.	Miscellaneous.	Total.
		Simple.	With phlebitis.		Simple.	With phlebitis.								
Total cases		21	4	13	27	4	13	1	2	3	4	2	6*	100
Degree of edema	Slight	16	..	11	18	..	3	..	1	2	..	..	2	52
	Moderate	5	3	2	8	4	6	1	1	1	3	..	3	37
	Marked	..	1	..	1	..	4	..	..	..	1	2	1	11
Age	Under 40	2	..	4	1	1	1	1	1	..	2	..	3	16
	40 to 60	18	2	8	19	3	3	..	1	2	1	2	2	61
	Over 60	1	2	1	7	..	9	..	..	1	1	..	1	23
Sex	Male	6	1	..	6	..	8	1	2	1	2	2	1	29
	Female	15	3	13	27	4	5	..	..	2	2	..	5	71
Heart disease		1	..	..	7	1	13	..	..	..	..	..	..	22
Hypertension		6	1	2	8	3	10	1	..	1	..	..	..	32

* One case of rheumatoid arthritis, 1 of carcinoma of the cervix with metastases to liver (marked edema), 1 of bilateral phlebitis of the femoral veins, 1 of myxedemal 2 in which no definite cause could be given for the edema.

was on careful inquiry found to be clearly due to obesity, age of the patient, or poor physical condition, and was moderate in most instances. On the other hand, when patients presented the symptom of orthopnea, congestive failure was the cause of their edema in all cases except 1 (cirrhosis of the liver with ascites). We feel that whereas a complaint of dyspnea, palpitation and precordial pain may be elicited in many of these individuals with varicose veins and at first suggests a cardiac etiology, a careful evaluation of these symptoms and a thorough physical examination often are

necessary to determine whether the edema is due to heart failure or not. A little time spent in a careful investigation of these cases will more than repay itself by more accurate diagnosis.

The Hospital Ward Group. (See Table 2.) The predominant cause for edema was congestive heart failure (60 cases). The reason for the difference between this group and that of the Out-Patient Department is that the majority of the sicker patients were admitted directly to the hospital. It will be seen that many of the

TABLE 2.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.
(Distribution of cases seen in Massachusetts General Hospital Wards.)

		Heart failure					Varicose veins.		Obesity.		Renal.							
							Without obesity.											
		Total.	Uncomplicated.	With varicose veins.	With obesity.	With nutritional deficiency states.	Simple.	With phlebitis.	Without varicose veins.	With varicose veins.	Acute nephritis.	Nephrosis.	Nutritional.	Cirrhosis of liver.	Leukemias.	Myxedema.	Miscellaneous.	Total.
Total cases		60	34	9	11	6	4	2	2	4	5	2	7	7	2	2	3*	100
Degree of edema	Slight	8	6	1	..	1	4	1	2	2	1	..	6	..	..	..	1	25
	Moderate	25	16	5	4	..	..	1	..	2	3	1	1	1	2	2	2	40
	Marked	27	12	3	7	5	..	..	..	..	1	1	..	6	..	..	..	35
Age	Under 40	14	7	1	6	..	..	..	..	..	4	2	2	1	..	1	1	25
	40 to 60	27	19	3	3	2	2	..	..	2	1	..	2	6	2	1	2	45
	Over 60	19	8	5	2	4	2	2	2	2	..	..	3	..	..	..	..	30
Sex	Male	38	28	3	3	4	4	1	1	3	2	2	5	5	1	1	1	64
	Female	22	6	6	8	2		1	1	1	3	..	2	2	1	1	2	36
Heart disease	Total	60	34	9	11	6	1	..	1	1	1	..	..	1	..	..	..	65
	Hypertensive	18	4	4	5	5	1	..	..	1	..	..	..	..	..	..	..	22
	Coronary	19	13	3	2	1	..	..	..	..	..	..	..	1	..	..	..	20
	Rheumatic	17	12	2	3	..	..	..	..	..	..	..	..	..	..	..	..	17
	Ch. cor pulmonale	4	3	..	1	..	..	..	..	..	..	..	..	..	..	..	..	4
	Luetic	2	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2

* One case of bilateral phlebitis of the femoral veins, 1 of rheumatoid arthritis, 1 of syringomyelia.

congestive failure cases were complicated. In the 6 cases in which heart failure was stated to be complicated by nutritional deficiency states, we have listed only those patients with evidence of severe deficiencies with low serum protein, and so on. Undoubtedly this is too low a figure, because many cases with congestive failure over a long period of time will have poor appetites and a dietary intake low in protein and lacking in vitamins. This quite likely is one reason why the usual treatment for congestive failure may in an occasional case not be completely effective.

The 7 cases caused by nutritional factors without heart failure included 3 instances of carcinoma of the stomach with poor dietary

intake, 1 of duodenitis and jejunitis with a very poor intake of food, bleeding gums, and a serum protein of 3 gm., 1 of regional ileitis with many operations, profound inanition and a serum protein of 4.4 gm., 1 of cancer of the lung, and 1 of chronic ulcerative colitis with a serum albumin of 2.9 gm. and globulin of 3.16 gm. per 100 cc.

Of the 2 cases of leukemia, 1 had chronic lymphatic leukemia with large glands in the inguinal region and some inanition which were probably the factors involved in the edema; the other had chronic myelogenous leukemia with infiltration of the liver and possibly some portal obstruction.

One case of syringomyelia of the cervical cord developed moderate edema. He was unable to use his lower extremities well and would sit in a chair for long periods of time. We were convinced that posture was the main cause of the edema in this instance.

The 30 remaining cases included 10 with varicose veins, 2 with obesity alone, 7 with cirrhosis of the liver, 5 with acute nephritis, 2 with nephrosis, 2 with myxedema, 1 with rheumatoid arthritis and 1 with bilateral femoral phlebitis.

A comparison of the out-patient and hospital groups is shown in Table 3.

TABLE 3.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.
(Comparison of the Chief Clinical Causes in 100 Out-patient Department and 100 Ward Cases of the Massachusetts General Hospital.)

Cause.	O.P.D. cases.		Ward cases.	
Varicose veins:				
Total	56		10	
Without obesity		25		6
With obesity		31		4
Heart failure:				
Total	13		60	
Uncomplicated		13		34
Complicated		..		26
Marked obesity alone	13		2	
Renal disease	3		7	
Nutritional	3		7	
Cirrhosis of liver	2		7	
Miscellaneous	10		7	
Total	100		100	

Discussion. Although this study has represented a fair cross-section of the various causes of edema, there are other factors to be considered. The effect of the upright posture in the production of edema needs emphasis. It is well known that the venous pressure in the ankles and feet in a standing normal individual may be very high (100 cm. or more).[2] Usually this is not important, because muscular movement in walking will promote both blood and lymph flow and thus compensate for such high hydrostatic pressures. However, if a normal person should stand in one position for an hour or more, slight edema of the ankles will occur.[2,3] Undoubtedly a number of old persons develop some edema of the lower extremities because they are inactive and sit for long periods. Many patients

who have been confined to bed for several weeks after an operation develop slight dependent edema during the first few days of convalescence. The presence of deep or superficial varicosities will increase, of course, the tendency to edema formation under such conditions. From a practical clinical standpoint, therefore, the factor of posture is an important one and should be considered in all cases of obscure edema.

The size of the patient's heart is a factor which must be given careful consideration. It is of considerable importance to realize that congestive heart failure does not occur without cardiac enlargement. Therefore, if we find the heart of normal size in the presence of edema of the legs we can rule out at once myocardial weakness and failure as the cause of such edema. The one interesting point about the possible relationship of a normal heart size with probable cardiac origin of the edema of the legs concerns the rare cases of chronic constrictive pericarditis in the series we are reporting herewith, but one should be on one's guard for such a case. If a patient with edema of the feet, or especially with enlargement of the liver and ascites, is encountered with normal heart size, engorged neck veins, and no obvious reason for the edema, one should think of the possibility of, and look for, constrictive pericarditis.

It is not within the scope of this paper to present in detail the pathologic physiology and mechanism of edema formation. This has been well discussed and summarized elsewhere.[1,2,4,6]

It becomes obvious, in view of our findings, that it is important to determine carefully the cause of edema in each individual case. Sometimes it will not be possible to do so, and after a careful study no clear-cut reason can be given for the edema, but in our experience such cases are exceptional. We would like to emphasize that when one is confronted with a case of edema, especially if it be slight or moderate, one should carefully determine the cause and not be too quick to attribute it to heart failure. Nor, on the other hand, should one say that the edema is due to some simple, relatively unimportant cause, unless an adequate study proves that to be true.

Summary. 1. Unselected cases of bilateral edema of the lower extremities (100 from the Out-Patient Department and 100 from the wards of this hospital) have been analyzed and the predominant causes of the edema and their frequency have been determined. In the out-patient group, which is analogous to a group of patients seen in general medical practice, the causative factors occurred in the following order of frequency: varicose veins (56 cases), with obesity (31 cases), without obesity (25 cases); obesity alone (13 cases); cardiac failure (13 cases); lymphedema (4 cases); renal disease (3 cases); nutritional factors (3 cases); cirrhosis of the liver (2 cases); and miscellaneous factors (6 cases).

2. The ward group showed the following frequency: congestive heart failure (60 cases); varicose veins or obesity alone or in com-

bination (12 cases); renal disease (7 cases); nutritional factors (7 cases); cirrhosis of the liver (7 cases); leukemia (2 cases); myxedema (2 cases); and miscellaneous factors (3 cases). The predominance of cases of heart failure in this group, in contrast to the former, is to be expected as only the sicker patients are admitted to the wards.

3. Thus it has been found that in an unselected group of ambulatory individuals with bilateral edema of the lower extremities, cardiac failure as an etiologic factor is less common than often thought. Varicose veins and obesity, with posture as a secondary or primary factor, are far more commonly responsible in such a group, particularly when the edema is slight or moderate in degree. Many such patients have symptoms which suggest a cardiac etiology, but careful study reveals that such symptoms are unrelated to organic heart disease and that the edema is the result of the less serious factors. We wish to emphasize that in a group of ambulatory patients, dependent edema infrequently indicates heart failure and therefore rarely requires digitalis therapy; such simple factors as varicose veins, obesity and posture, alone or in combination, are much more commonly the cause of the milder degrees of edema in such cases than is heart disease.

REFERENCES.

(1.) **Fishberg, A. M.**: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934. (2.) **Harrison, T. R.**: Failure of the Circulation, Baltimore, The Williams & Wilkins Company, 1935. (3.) **Holling, H. E., Beecher, H. K.**, and **Linton, R. R.**: J. Clin. Invest., **17**, 555, 1938. (4.) **Landis, E. M.**: Ann. Int. Med., **10**, 290, 1936. (5.) **Linton, R. R.**: Personal communication. (6.) **Smirk, F. H.**: Clin. Sci., **2**, 317, 1936.

"PIGEON DERMATITIS," A VITAMIN B DEFICIENCY STATE WITH ANEMIA.*

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The classical experiments with beri-beri have been chiefly performed in pigeons.[31] When these animals are fed on a diet of polished rice, and at the same time given injections of thiamin chloride (vitamin B_1), the development of beri-beri is prevented.[32] Upon continuance of this régime, characteristic symptoms develop in the course of 4 to 12 weeks. The animals lose considerable weight and

* Aided by grants from the Commonwealth of Massachusetts, the Rockefeller Foundation, and W. P. A. Project 18088.

stand quietly for hours at a time with head on chest. The feathers become "fluffed out" and dirty in appearance, and the horny covering of the beak, legs and claws becomes dull and thickened. After 12 to 15 weeks, a well-marked anemia develops in association with hyperplasia of the marrow. The anemia and all the symptoms of this deficient state respond to therapy with liver extract and yeast, but no effect occurs when riboflavin, nicotinic acid, or the rat anti-dermatitis principle (vitamin B_6) is administered. In many respects, the clinical picture of the deficiency corresponds closely to that of "chick pellagra" as described by Elvehjem *et al.*[16] The present communication deals chiefly with the clinical, hematological, and bone-marrow findings of this deficiency state and with the therapeutic effects of certain agents.*

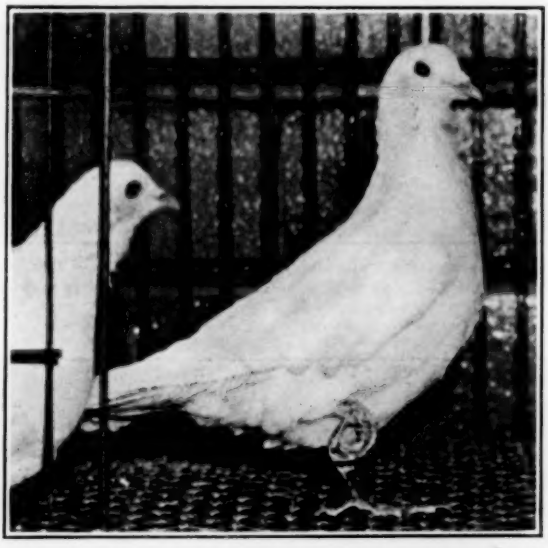

FIG. 1.—Normal pigeon. Note the "proud" erect position, and the sleek, smooth feathers.

Methods and Materials. White king pigeons, weighing from 300 to 550 gm. were used. After a preliminary period of observation of 2 weeks, during which time the animals were on a corn and grain diet, the diet was completely restricted to polished rice and water. This resulted in beri-beri within 2 to 4 weeks. To obtain a state of vitamin B_2 complex deficiency, vitamin B_1 was given by regular daily injections simultaneously with in-

* We are indebted to Drs. Leo Alexander, Abraham Myerson, and Michel Pijoan for permission to utilize their pigeons (Series I, II, III, IV) for hematological studies. Dr. Alexander performed many of the postmortem examinations and Dr. Pijoan prepared riboflavin phosphate and "yellow ferment." Neurological studies in the deficient pigeons have been made by the above workers and a preliminary report was recently published (Trans. Am. Neur. Soc., **64**, 135, 1938). Other articles dealing with the neurological features of the deficiency state by the same authors are in preparation.

duction of the polished rice diet. The animals were weighed twice weekly and frequent observations were made of their physical status.

Blood studies were made weekly until the pigeons became anemic and at more frequent intervals when therapy with a specific substance was employed. The method of obtaining blood for examination in pigeons is

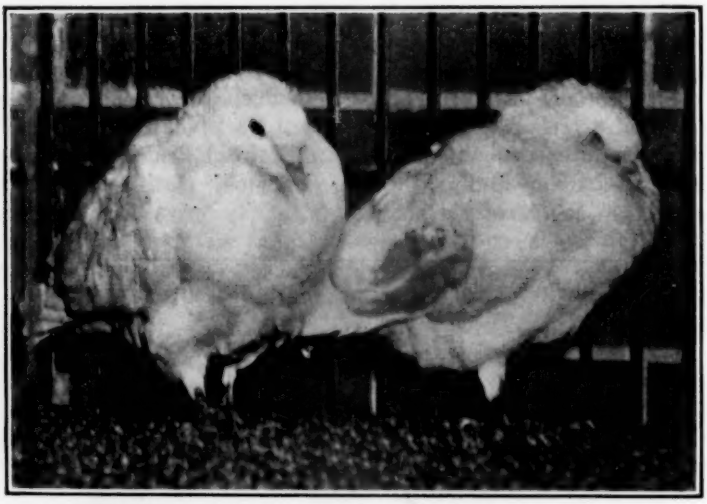

FIG. 2.—Two pigeons with vitamin B_2 complex deficiency. The pigeons stand quietly for hours with heads on chest; their feathers become dirty and "fluffed out," and keratinization of the beak and legs develop.

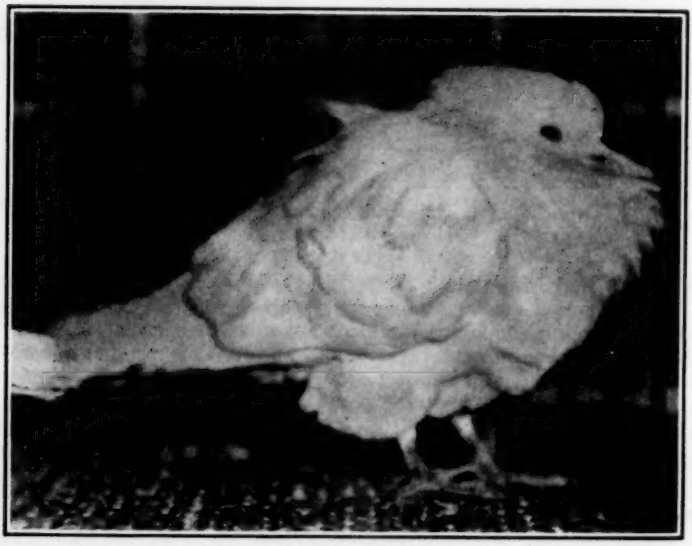

FIG. 3.—Pigeon with vitamin B_2 complex deficiency. Note the marked "fluffed out" appearance of the feathers.

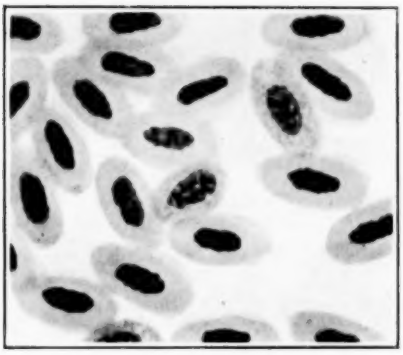

FIG. 4.—Photomicrograph of a blood smear (× 1520) of a normal pigeon stained with brilliant cresyl blue and Wright's stain. Note that the nuclei of the reticulocytes are larger, rounder and less pyknotic than those of the non-reticulated erythrocyte.

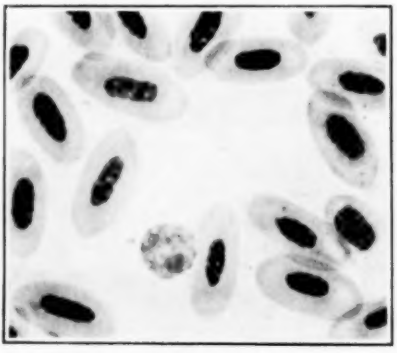

FIG. 5.—Photomicrograph (× 1520) of stained blood smear of a pigeon with an induced B_2 complex deficiency state and severe anemia. Note the variation in size of the individual red cells. The nuclei show marked differences in size, shape, staining characteristics, and position.

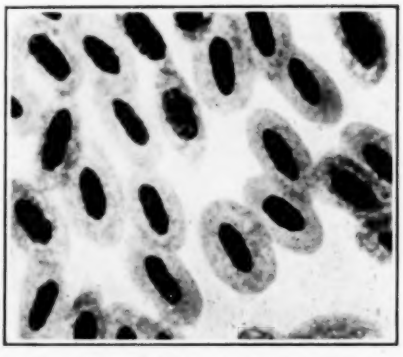

FIG. 6.—Photomicrograph (× 1520) of reticulocyte preparation from a vitamin B_2 deficient pigeon (Series VI, No. 17) 5 days after the administration of a dilute liver extract was begun. The reticulocyte count was 95% (!). Occasional reticulocytes are small, thick and heavily-stained.

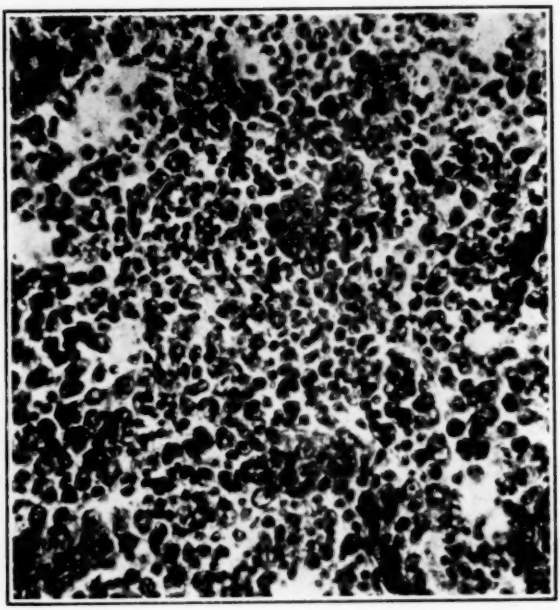

FIG. 7.

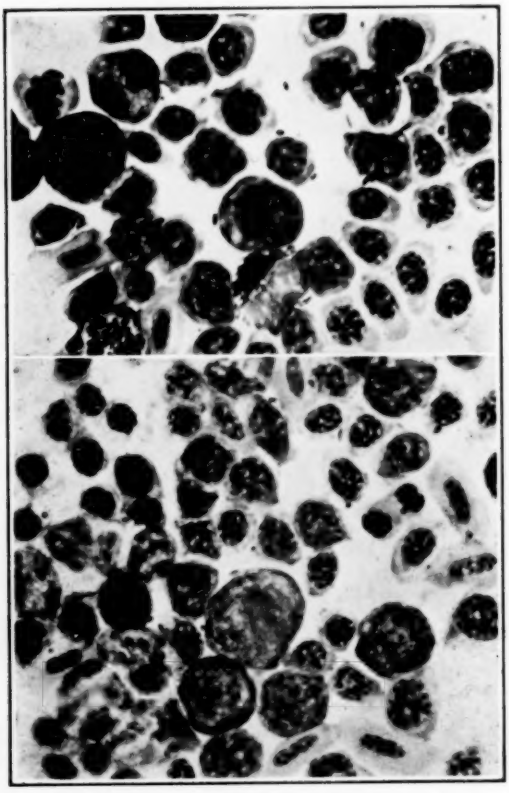

FIG. 8.

important and has not been sufficiently described in other publications dealing with the hematology of pigeons. Puncture of one of the large vessels under the wing was often attended with the loss of considerable blood, and at times exsanguination. The loss of blood attending such a procedure might well account for the considerable fluctuations in the reticulocyte counts of normal pigeons as noted by other investigators. On the other hand, use of one of the very small, just visible vessels nearby the large wing vessels, although occasionally successful, usually resulted in failure to obtain sufficient blood. An accidental puncture of the skin of the leg led to the discovery that good-sized, readily controlled drops of blood could be obtained from a small nick in the "red" skin of the leg.

Because of the well marked tendency of pigeon's blood to clot rapidly, two individuals are necessary in taking blood for counts. With the first drop, blood for hemoglobin is obtained, and immediately thereafter the red cell pipette is quickly filled by the second technician, following which smears are obtained. Pressure is then made over the puncture, which is covered with a bit of absorbent cotton.

Blood for hemoglobin, red blood cell count, and reticulocyte count was obtained. The hemoglobin was at first determined by the Sahli method (calibrated so that 100% = 15.5 gm.), and in the more recent and detailed experiments, by the Evelyn photoelectric method (100% = 15.6 gm.). The red cell counts were performed with United States Bureau of Standards pipettes and hemacytometers. Hayem's solution was found unsatisfactory because of its tendency to cause a murky solution with the pigeon's blood (hyperproteinemia?). On the other hand, a solution of sodium citrate 1.5% gave clear suspensions, and the tendency to clot formation within the pipette was prevented. Reticulocyte smears were made by preparing cover slips with a film of 1% alcoholic solution of brilliant cresyl blue, the usual 0.3% solution being found unsatisfactory, probably because of the greater absorption of dye by the nuclei of the red cells. Blood smears were made in the ordinary way and counterstained with Wright's stain—stain 1 minute, water 1 minute. If the second step in staining was longer than 1 minute, reticulocytes were frequently not visible, being now represented as polychromatophilic red cells. The staining of the reticulum substance was at times a variable phenomenon, and even with the utmost care, smears were occasionally obtained with polychromatophilic cells rather than reticulocytes. Furthermore, the reticulocytes at times exhibited variability in staining *even in the same smear*. In counting these cells it was absolutely essential to deal only with those sections of the smear in which the reticulocytes were well stained.*

* Nittis[24] has recently criticized the findings of previous workers with pigeons' reticulocytes. He rightly points out that in fresh preparations practically all the erythrocytes are reticulated. However, with the use of Dameshek's reticulocyte-platelet solution,[6] it is easily possible to distinguish the dense highly reticulated reticulocyte from those red cells which show only scattered granules. In "dry" preparations, the differentiation between reticulocytes and non-reticulocytes is readily made, not only by the reticulum present in the reticulocytes, but by distinct differences in morphology of the nuclear structure. These points will be covered in another communication.

LEGENDS FOR FIGS. 7 AND 8.

FIG. 7.—Photomicrograph (× 450) of femoral bone marrow section (Zenker's fixation; eosin-methylene blue stain) of a pigeon dying of vitamin B_2 deficiency. Note the marked cellularity of the marrow with the presence of large islands of primitive erythroblasts (erythrogones). This marrow resembles that of human pernicious anemia.

FIG. 8.—Photomicrographs (× 1320) of stained bone marrow smear from pigeon dying of vitamin B_2 deficiency. The large primitive cells are erythrogones and they are surrounded by early nucleated red cells (normoblasts A and B or pronormoblasts and erythroblasts).

Postmortem examinations were made of all pigeons which died. Particular attention was paid to the bone-marrow, although sections of the spleen, liver, and occasionally of other tissues were obtained. Bone-marrow (in "cylinders") was removed from the ulnas and femurs. Impression smears were immediately made from portions of these marrows and stained with Wright's stain (stain 6 minutes, stain and water 30 minutes). From these preparations, the morphology of the individual cells is readily studied and differential counts made according to the method of Dameshek and Valentine.[7] The following nucleated red cells are discriminated: Erythrogone (primitive nucleated red cell); Normoblast A (basophilic cytoplasm, but with definite red cell characteristics); Normoblast B (containing hemoglobin but not completely matured); Normoblast C (mature marrow erythrocyte). The entire cylinder of marrow was fixed in Zenker's solution, containing 5% of glacial acetic acid, and the sections stained with eosin-methylene blue.

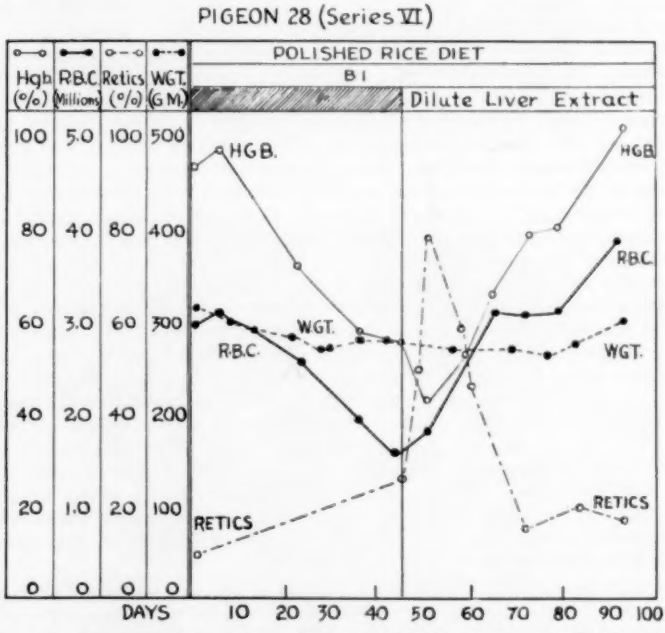

CHART I.—Pigeon 28 (Series VI). On a diet of polished rice with added thiamin there was progressive anemia. Following the injection of a dilute liver extract, a marked reticulocytosis developed, which was followed by increases in hemoglobin and erythrocyte counts above their original values.

The following materials were utilized during the course of the experiments:

1. *Vitamin B_1* (thiamin chloride) (Winthrop Chemical Company, "Betaxin"): 1 mg. tablets (containing 300 I.U.) were dissolved in 10 cc. distilled water. One cubic centimeter of this solution (containing 0.01 mg. of thiamin chloride) when injected intramuscularly every 2 days was more than adequate to prevent the development of beri-beri and was curative for beri-beri when this developed.

2. *Riboflavin.* (*a*) Riboflavin (Hoffmann-LaRoche, synthetic) given daily by intramuscular injection in dosage of 0.02 mg. (*b*) Riboflavin phos-

phate (phosphorolized for us by Dr. Michel Pijoan) in daily injections of 0.02 mg. intramuscularly. (*c*) "Yellow ferment"—daily intramuscular injections of 0.001 mg.

3. *Nicotinic acid* (Merck) given daily by intramuscular injection in dosage of 2 mg.

4. *Rat Anti-dermatitis Principle* (Vitamin B_6). (*a*) *Crude*, obtained from yeast and prepared according to the method of Lepkovsky and Jukes,[18c] given daily by intramuscular injection in dosage of 0.5 cc. (*b*) *Factor 1* (Lepkovsky[17])—crystalline. This pure material was kindly supplied by Dr. Lepkovsky and was given intramuscularly in daily dosage of 0.5 cc. (0.05 mg.).

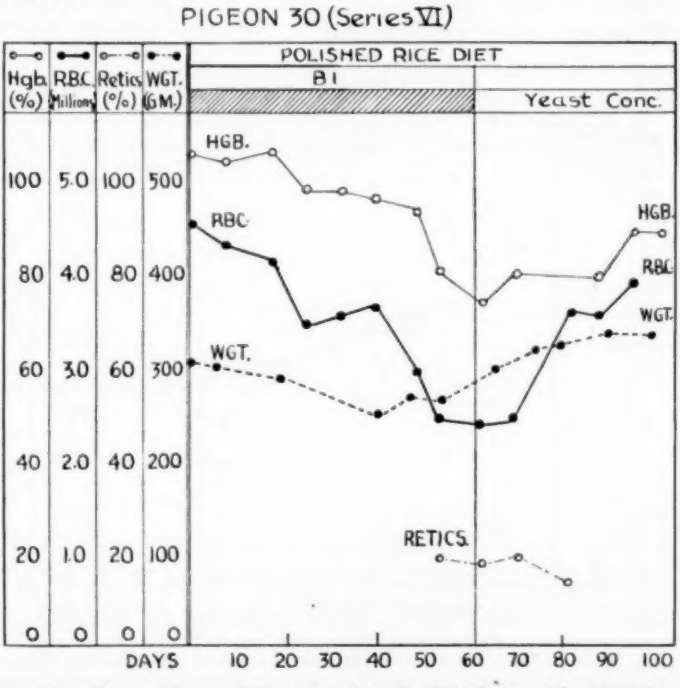

CHART II.—Pigeon 30 (Ser. VI). On a diet of polished rice with added thiamin, progressive anemia developed; this was readily controlled by the administration of yeast concentrate tablets orally.

5. (*a*) *Chick Anti-dermatitis Factor* (Elvehjem).[35,20] This purified (colorless) material was kindly supplied by Dr. Elvehjem and was given intramuscularly in dosage of 0.5 cc. every other day. (*b*) *Filtrate Factor(s)* or *Factor 2* (Lepkovsky). This material (a heavy brown liquid) was kindly supplied by Dr. Lepkovsky and was given orally in dosage of 0.5 cc. daily.

6. *Vitamin B Parenteral* (Lederle). According to the manufacturer each cc. contains besides B_1, riboflavin 0.3 mg. (100 B-S units), nicotinic acid, dermatitis factor(s) 30 "rat day" units, and filtrate factors, approximately 30 "chicken day" units.

7. *Liver Extracts:* (*a*) Lilly "concentrated" liver extract for parenteral use. A relatively dilute extract of liver, 1 cc. being derived from 10 gm. of whole liver and containing 2 USP units per cc. Dosage 0.5 cc. by daily intramuscular injections. (*b*) Lilly "reticulogen" for parenteral use.

A highly purified and concentrated extract of liver, 1 cc. being derived from 100 gm. of whole liver. Dosage 0.5 cc. by intramuscular injection every 2 days.

8. *Yeast Concentrate Tablets* (Mead's Brewers Yeast Tablets). 1 tablet (389 mg.) given orally, daily.

9. *Vitamin C*, ascorbic acid, synthetic (Hoffmann-LaRoche) 25 mg. given orally every 2 days.

10. *Iron citrate* injectable (Parke-Davis), 0.25 cc. given daily by intramuscular injection (containing 0.025 gm. of Fe citrate).

Results. NORMAL PIGEONS AND NORMAL CONTROLS. The normal pigeon is lively, moves about freely in his cage, and has smooth, clean feathers, which are "unruffled." The beak and the epidermis

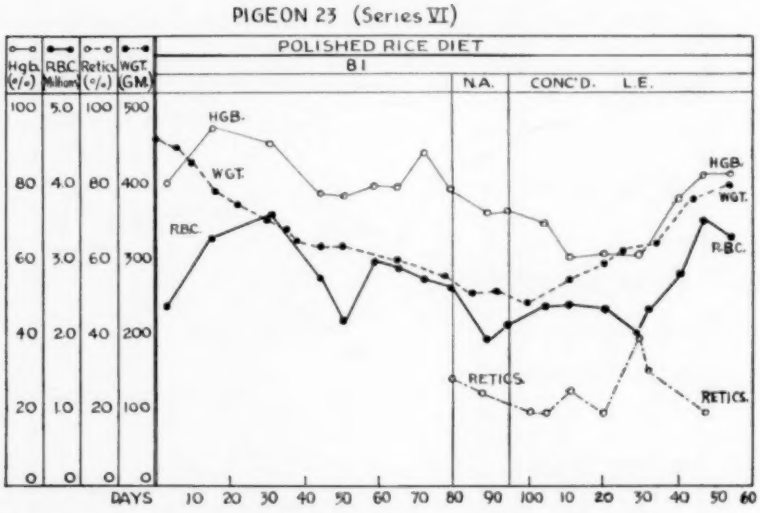

CHART III.—Pigeon 23 (Ser. VI). On a diet of polished rice with added thiamin, there were progressive reductions in hemoglobin, red cell count, and weight. Nicotinic acid given parenterally failed to stay the progress of the deficiency state, which was finally benefited by the persistent use of a highly purified and concentrated liver extract.

of the legs are smooth and of good color. The blood findings in our pigeons showed the following ranges: Hemoglobin (45 observations) 77 to 122%, average 92.8%; red cell count 2.24 to 4.57 (46 observations), average 3.22 millions; reticulocytes (40 observations) 10.8 to 14.6%, average 12.4%. Careful inspection of the nuclei of reticulocytes and non-reticulocytes disclosed that the nuclear structure in the non-reticulocyte (mature cell) is much more compact and pyknotic than in the relatively immature reticulocyte. In the latter cell, the nucleus is wider and larger and clear spaces in the nuclear structure are usually visible. The normal bone marrow is extracted from the femurs and the ulnas as firm, reddish cylinders.

The femoral marrow is normally red throughout its extract, but the ulnar marrow is usually fatty or flecked with reddish material. Differential counts of normal marrow impression smears (500 cells counted) give approximately the following findings:

Femur: Erythroblastic cells:	Per cent.	Ulna: Erythroblastic cells:	Per cent.
Erythrogones	2	Erythrogones	1
Normoblasts "A"	10	Normoblasts "A"	2
Normoblasts "B"	10	Normoblasts "B"	2
Normoblasts "C"	25	Normoblasts "C"	50
Mature erythrocytes	20	Mature erythrocytes	24
Leukocytes	33	Leukocytes	21

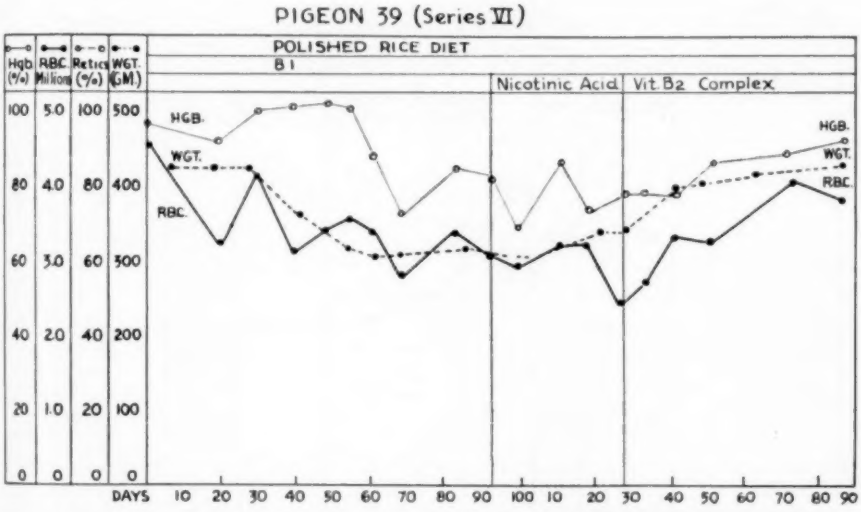

CHART IV.—Pigeon 39 (Ser. VI). Nicotinic acid was of no value in the treatment of the B_2 deficiency state, which was rectified by the administration of vitamin B complex given parenterally.

A detailed description of these cells is given in the paper of Dameshek and Valentine.[7] The smears from the femur were far more cellular and of better quality than those from the ulna; in many cases, the latter were too fatty to be properly stained or counted.

Sections of the normal marrows stained with eosin-methylene blue showed: *Femur:* A full, actively growing marrow with large groups of erythrocytes and leukocytic cells arranged in islands. The "blue" islands were for the most part early erythroblastic cells; these were usually in groups; the "red" islands, mostly granulocytes. Orderly maturation of cells from the most primitive to the most mature was clearly seen. Running throughout the section were always found branches of bone-marrow blood-vessels containing large numbers of closely packed mature erythrocytes. *Ulna:*

usually composed of one-half to two-thirds fat with small foci of both red and white cells. The vascular branches, containing mature, elongated, nucleated red cells, were quite prominent in these sections.

STARVATION (Series II). Complete starvation of the normal pigeon resulted in varying degrees of hypoplasia of the marrow. At the same time, the marrow of both the femur and ulna often took on a "disorganized" edematous appearance with the presence of fibrous tissue strands as a prominent feature. The degree of hypoplasia was subject to much individual variation. No blood studies were carried out in this series.

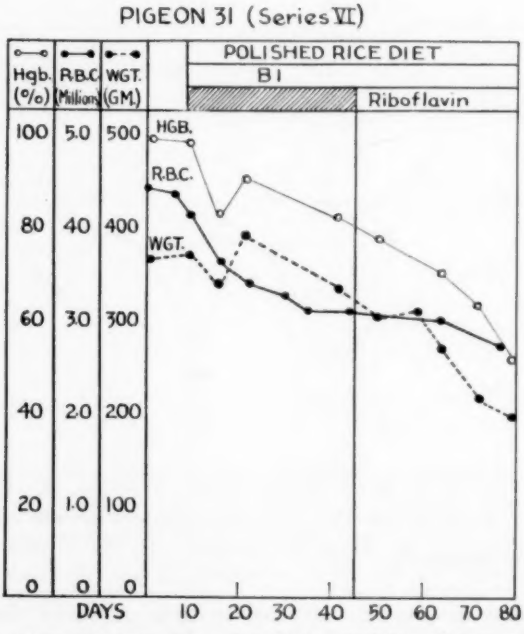

CHART V.—Pigeon 31 (Ser. VI). Riboflavin administered parenterally was of no value in the treatment of the B_2 deficiency state induced by a diet of polished rice with added thiamin.

COMPLETE B_1 AND B_2 DEFICIENCY (Beri-beri) (Series IV). These animals died of classical beri-beri within 2 to 4 weeks. The condition of the marrow was variable, although marked changes were always present. In most cases, an edematous disorganized marrow was present with hypoplasia of the erythroblastic tissue. Usually, even with well-marked hypoplasia, islands of primitive cells interpreted as erythrogones were present. In some cases, these islands were quite prominent giving the appearance of hypercellularity; in these instances, the more mature forms of nucleated red cells were greatly diminished (*i. e.*, maturation arrest?). Large numbers

of small, round cells (lymphocytes? thrombocytes?) were often seen and at times the appearance of well marked lymphoid infiltration was presented. Evidences of increased blood destruction were usually present, *i. e.*, hemosiderosis, erythrophagocytosis of hemosiderin or broken down red cells by large cells (probably histiocytes). The leukocytic tissue, by contrast with the hypoplastic erythroblastic tissue, was usually very prominent and this apparent hyperplasia often resembled that due to infection.

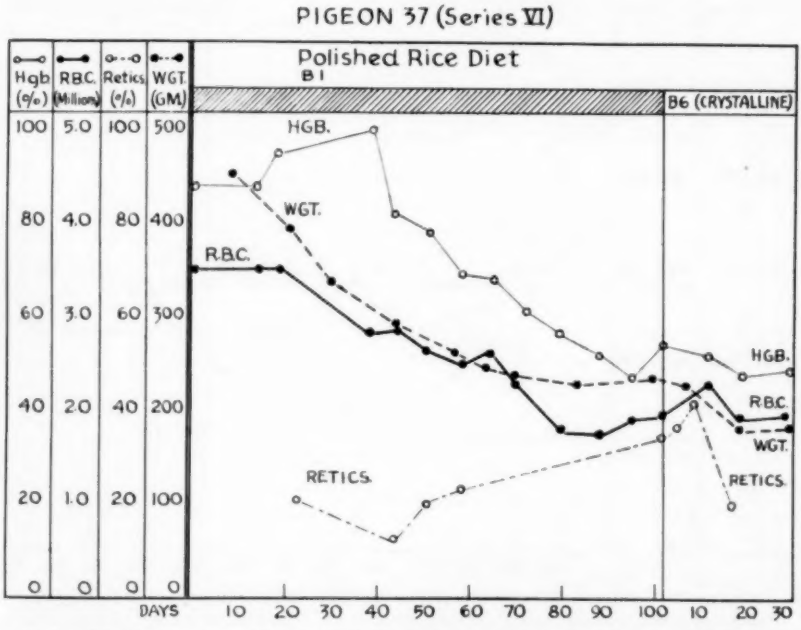

CHART VI.—Pigeon 37. The rat anti-dermatitis principle—vitamin B_6 crystalline—was of no definite effect in the amelioration of the B_2 deficiency state.

Blood studies of the pigeons with beri-beri were made in Series VI. Slight anemia developed, marked more by a reduction in hemoglobin than in the erythrocyte count. The average reduction in hemoglobin (10 birds) was 13.3% in an average time of 14.6 days. The erythrocyte count in the same birds dropped on the average only 0.17 million. In some birds, an actual increase in red cell count occurred. The accuracy of the counts in pigeons with beri-beri must be questioned in view of the marked changes in water balance which must inevitably take place. Furthermore, the apparent rise in red count of some of the pigeons may be due to dehydration, since with onset of beri-beri some of the birds became indifferent to their surroundings and did not take water.

To summarize, the bone marrow of the pigeons dying of beri-beri

generally showed evidences of hypoplasia with foci of primitive red cells (maturation arrest?) and at times hyperplasia of leukocytic tissue. Slight anemia usually developed, although the accuracy of blood counts in beri-beri is to be questioned in view of possible changes in water metabolism.

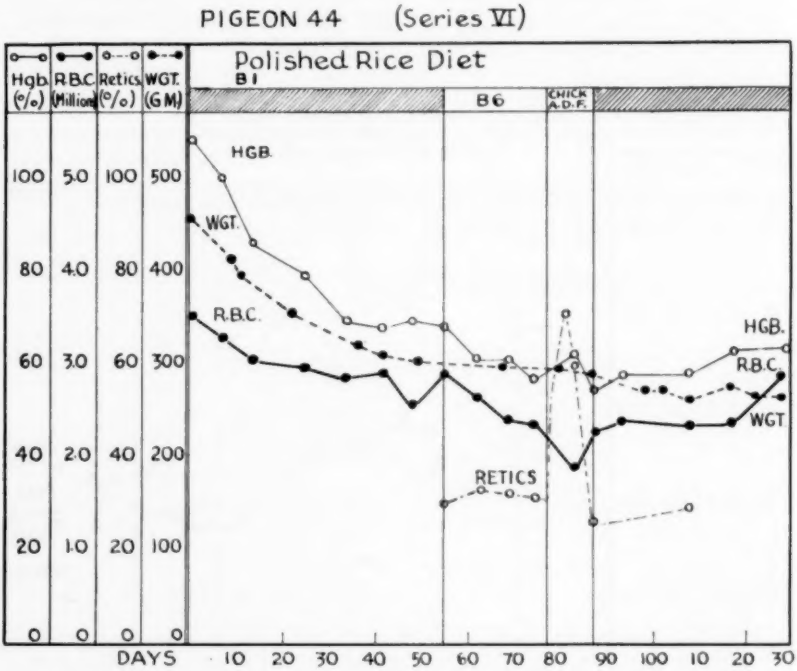

CHART VII.—Pigeon 44. Vitamin B_6 (crystalline) did not improve the B_2 complex deficiency state, nor did reticulocytosis develop. Upon administration of the chick anti-dermatitis principle, as purified by Elvehjem, a reticulocytosis ensued which was, however, not followed by an increase in the hemoglobin or red cell count nor by improvement in the pigeon's physical status.

B_1 DEFICIENCY. In 3 pigeons (Series IV, Group 4), a yeast extract free of B_1 was given simultaneously with the diet of polished rice, *i. e.*, beri-beri developed, although the B_2 complex was probably present in adequate amounts. In 1 of these animals, there was well marked red cell formation; in the other 2, hypoplasia of erythroblastic tissue was prominent. No blood studies were made in these animals.

B_2 COMPLEX DEFICIENCY. Pigeons fed on a diet of polished rice and water and simultaneously given daily injections of thiamin chloride (Vitamin B_1) intramuscularly, lost weight fairly rapidly. The symptoms of beri-beri did not develop. For 2 to 4 weeks, the animals presented a fairly normal appearance, but between the 4th to 12th week, definite clinical changes became noticeable in most of the

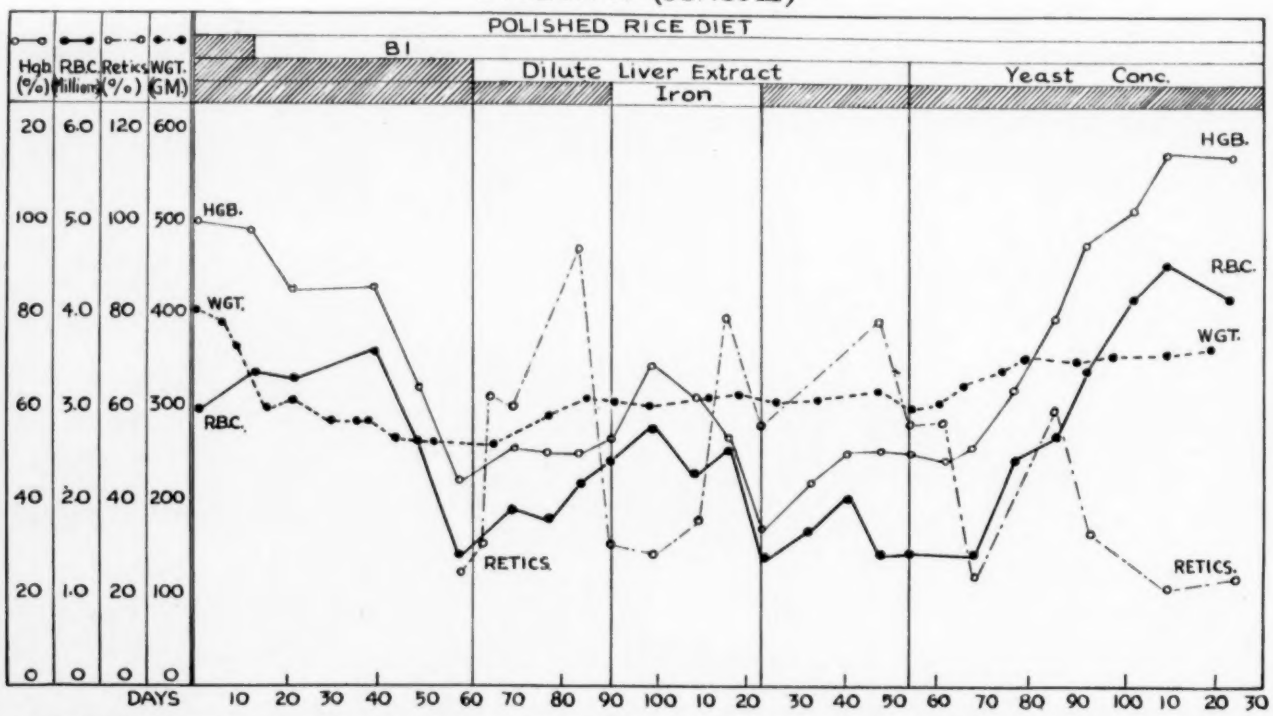

CHART VIII.—Pigeon 17. A well-marked anemia developed on a diet of polished rice with added thiamin. Administration of a dilute liver extract resulted in a marked reticulocytosis and a definite increase in red cell count. Because of the lag in hemoglobin value, iron was added by parenteral route; this resulted in a temporary increase in hemoglobin but was followed by a toxic reaction. Liver extract was continued but without effect; when yeast concentrate was then given orally, a striking response clinically and hematologically ensued.

animals. They appeared listless, stood quietly in their cage, usually with head bent on the chest. Shivering spells were often noticed. The feathers, normally clean, sleek, pure white, and closely applied to each other, became unkempt, dirty-gray, and irregularly "ruffled" or "fluffed out." As the deficiency developed, definite changes became noticeable in the beak, claws, and epidermis of the legs. The normally smooth, red appearance of these parts became lost and the epidermis developed an irregular, dirty, brownish, hyperkeratinized appearance. There was slow progression of symptoms for 3 to 6 months, and unless specific therapy was begun, death occurred usually within the 6-month period.

With development of this deficiency state, anemia gradually developed (in 17 of 20 pigeons in Series VI). A definite anemia was discernible between 28 and 90 days (average 52 days). Anemia became most marked from 41 to 107 days following the induction of the deficiency (average time 66.2 days). At this time, some sort of therapy was usually begun so that the lowest possible level of anemia which might develop was not determined. The hemoglobin at this time varied from 39 to 76% (average 58.2%), and the erythrocyte count from 1.28 to 2.69 millions (average 2.01 millions). The color index in these cases was always high, although the significance of this factor in the blood of pigeons is questionable. Estimations of the hematocrit and the mean corpuscular volume were not made. At the height of the anemia there was well-marked variation in size and shape of the red blood cells with the presence of many small "polychromatophilic" cells with deeply basophilic cytoplasm (corresponding to the presence of nucleated erythrocytes in human anemia?). The erythrocytic nuclei, normally pyknotic and situated longitudinally in the cell parallel to its long axis, not uncommonly became transversely placed. The strands of nuclear chromatin also became less well-defined (immaturity). The reticulocyte count usually increased to levels of between 20 to 30%. No particular changes in the leukocytes or thrombocytes were evident, although at times a well-marked increase in granulocytes was present. The appearance of the bone-marrow of pigeons dying of this deficiency was variable, depending in most part upon the duration of the deficiency state. Of 20 marrows examined completely, 9, from pigeons with long-standing deficiency and well-marked anemia, showed essentially the same picture. This was characterized by well-marked cellularity, the presence of many primitive cells classed as erythrogones, and marked increase in early red blood cells.

Differential count of the bone-marrow smear in a typical case (Series V, Group XI, Pigeon 2) showed the following: Ratio of R.B.C. to W.B.C. 1:0.18. The red cells were differentiated as follows:

	Per cent.
Primitive R.B.C. (erythrogones; normoblasts "A")	27.2
Normoblasts "B"	37.4
Normoblasts "C"	21.0
Mature R.B.C.	12.4

In counting 500 R.B.C. 18 mitoses were seen.

Normal marrows in this group of B_2 deficiency were found when the birds were sacrificed at 9 days and 12 days respectively. After this period, and until well-marked anemia was present, the picture was variable, the marrow being either essentially normal, hypocellular, or hypercellular in appearance. Occasionally, a very marked leukocytic hyperplasia suggesting leukemia was present. In 2 birds dying suddenly during the course of this experiment, this possibility was definitely present in view of the very large spleen and the bone-marrow picture.

Effects of Various Substances on the B_2 Deficiency State. *Riboflavin and Riboflavin Phosphate.* In Series I, II, III, and V, 15 animals were given these substances simultaneously with the development of the deficiency and the marrows studied at death. These showed great variability from animal to animal in the same group, although there was usually a curious picture of marked hypoplasia with the presence throughout of finger-like vascular channels filled with mature red blood cells. In 3 pigeons (Series VI) given injections of riboflavin or its phosphate during the development of the B_2 deficiency state, there was continued and progressive clinical and hematological decline. The effect of this substance may be said to be entirely negative in these experiments.

Nicotinic Acid. In Series VI, 3 pigeons given injections of nicotinic acid during the course of the B_2 deficiency state showed a continued and progressive decline in their clinical and hematological status.

Vitamin B_6. Crystalline vitamin B_6 in solution was obtained from Lepkovsky and administered parenterally to 3 deficient pigeons in Series VI. No responses either clinically or hematologically took place.

"*Filtrate Factor*" (Lepkovsky). This material, a heavy brown liquid, was obtained from Lepkovsky, and administered orally to 2 deficient pigeons in Series VI. No responses occurred.

"*Chick-dermatitis*" *Factor* (Elvehjem). This material, a colorless solution, was obtained from Elvehjem and administered parenterally to 2 deficient pigeons in Series VI. Although reticulocyte responses took place, there was no definite clinical improvement and no increase in erythrocytes. Further experiments with this substance are planned.

Vitamin B Complex (parenteral, Lederle) (Series VI). Three deficient pigeons given this material by injection showed a slow, though definite improvement in clinical and hematological status. In Pigeon 11 (Series VI), following a slight response to this medication, the administration of yeast resulted in a marked response.

Liver extract, relatively dilute (Lilly "concentrated"). In all the 4 pigeons given this material parenterally, there was a striking response. There was rapid improvement in clinical status with marked gain in weight, reappearance of the normal alert appear-

ance, disappearance of the "fluffed out" and dirty appearance of the feathers, and replacement of the hyperkeratinized epidermis of the beak and claws by normal skin. Before the onset of clinical improvement, and within 2 to 5 days after the beginning of injections, there was an extreme reticulocytosis of 60 to 85% with the appearance of many "polychromatophilic" red cells. This picture was shortly followed by an increase in the erythrocyte count and a somewhat slower increase in the hemoglobin concentration. When iron was given to 2 animals in which hemoglobin production appeared to lag, there was a definite (temporary) increase in hemoglobin production (see under iron). Associated with the change to normality of the blood counts, there was an associated change to normality of the red blood cells in the stained preparations. In 1 animal (Series VI, No. 17) which had become very anemic after iron administration ("toxic" reaction), liver extract resulted in a marked and sustained reticulocytosis, which was, however, not followed by an increase in the red cell count. When yeast was then given orally, there was a rapid increase in the erythrocyte count.

Liver extract, highly concentrated (Lilly "Reticulogen"). Two pigeons with B_2 deficiency were given injections of "Reticulogen." There was a slow but progressive improvement in the clinical status in both, and a very slow but definite hematological response in one. In one of the pigeons (Series VI, Pigeon 14), a well-marked response occurred when injections of the relatively dilute liver extract were substituted for the concentrated material.

Yeast. A yeast concentrate was given by mouth to 4 pigeons with uniformly excellent results. In each instance, there were striking clinical and hematological effects. When yeast concentrate was given to a pigeon (Series VI, Pigeon 11), which had shown only a slight response to parenteral B complex, a rapid rise in both hemoglobin and red cell count took place. In another pigeon (Series VI, Pigeon 17), there was a well-marked erythrocyte response to yeast after liver extract had resulted only in reticulocytosis. Continuance of yeast therapy resulted in extremely high hemoglobin and erythrocyte levels.*

Iron. A solution of iron citrate was given parenterally to 2 pigeons in which hemoglobin production following liver extract injections appeared to be lagging behind erythrocyte formation. In both instances, there was a quick rise in hemoglobin, which was, however, followed by definite toxic effects as indicated by vomiting, weakness, rapidly progressive anemia and reticulocytosis (hemolytic anemia?). These symptoms improved upon continuance of iron therapy.

Discussion. A. *Pigeon "Pellagra" or "Dermatitis."* The pigeon has been the classical animal used in the study of beri-beri, B_1

* The administration of yeast to normal pigeons (in a preliminary study) has resulted in definite increases in hemoglobin and erythrocyte values.

deficiency.[31] The response to thiamin chloride in animals made B_1 deficient by a diet of polished rice is a striking one and has been the subject of many publications.[32] Definite deficiency states relating to the various elements of the B_2 complex have also received much attention. At the present writing, riboflavin, nicotinic acid, and vitamin B_6 (the rat anti-dermatitis principle), have been isolated in pure form and their deficiency states well described. Other deficiencies in various factors of the B_2 complex, not so well-defined, have also been described. In 1930 "Norris and Ringrose reported the development of a pellagra-like syndrome in chicks placed on a normal diet except for the use of powdered egg-albumin in place of the more common protein of animal origin. . . . The addition of 5% of autoclaved yeast prevented the symptoms."[9] In 1932, Kline, Keenan, Elvehjem and Hart[16] produced similar symptoms in chicks ("chick-pellagra"), which were given a diet of natural foodstuffs heated dry at 95° to 100° C. for 144 hours. No symptoms developed when the diet was supplemented with 0.8% of dilute liver extract (Lilly 343). Elvehjem and his collaborators then set about the task of isolation of this "anti-pellagra" factor and soon found that flavin and the "anti-pellagra" factor must be separate substances.[10] The inefficacy of the flavins in both chick and human pellagra was soon demonstrated. Lepkovsky and Jukes[18c] almost simultaneously made much the same observations and introduced the term "filtrate factor"[18c] for the material which was active in the prevention and treatment of chick pellagra. For some time, Elvehjem believed that the chick pellagra factor was identical with that active in dog black tongue and in human pellagra, but his recent work[11] and that of others with nicotinic acid demonstrated conclusively that the latter was the deficient factor in dog black tongue and in human pellagra.[26,28] The chick-pellagra factor, or better the chick anti-dermatitis factor* is thus not nicotinic acid and as yet has not been isolated in completely pure form. However, recent fractionation studies of Elvehjem and his collaborators[20,35] have shown considerable progress in this direction.

Thus, riboflavin, nicotinic acid (P-P factor), vitamin B_6 (rat anti-dermatitis principle, Factor 1 of Lepkovsky) have been isolated in pure form and their deficiencies described. Chick dermatitis and the chick anti-dermatitis principle are well along in description and isolation. Other less well-defined factors, and others perhaps undiscovered also exist in the B_2 complex.[9] Thus, Vitamin B_3 and Vitamin B_5 have respectively been described as weight-maintaining and weight-gaining factors in pigeons and Vitamin B_4 may be of some significance in a specific paralysis in chicks and pigeons. Reader[25] stated in 1929 that a tendency of the animal to sit in a hunched position was characteristic of a deficiency in this vitamin. The so-called Factor W[12] may also be of some importance.

* The Committee on Vitamin Nomenclature has ruled that the term "pellagra" should be used only in cases of humans.

Our work with pigeons has demonstrated that deficiency in the entire B_2 complex results (1) in a clinical state resembling chick dermatitis and which may be called pigeon dermatitis; (2) in anemia characterized by reduction in both hemoglobin and erythrocyte count but particularly in the latter; and (3) failure of response of either anemia or dermatitis to riboflavin, nicotinic acid, vitamin B_6 (rat anti-dermatitis principle); and the "filtrate factor" of Lepkovsky; (4) striking response to dilute liver extract and to yeast and a possible response to the purified chick anti-dermatitis factor of Elvehjem. Other substances in the B_2 complex, namely Factors B_3, B_4, B_5, various combinations of factors, or unknown factors may be implicated. There can be no doubt that the pigeons in these experiments were deficient in these factors, but for want of pure extracts of these substances, nothing definite can be stated regarding their relationship to the deficiency produced. The reticulocyte response with Elvehjem's chick dermatitis factor may indicate that this substance, *together with some other*, is implicated. The complete lack of response to a closely comparable substance—"filtrate factor"—is peculiar and indicates that these substances are not identical.

B. *Pigeon Anemia.* It is evident that a definite anemia develops in pigeons kept on a diet of polished rice supplemented with injections of thiamin chloride. This anemia is compatible with life over a period of several months and is not simply a terminal event. Indicative of the fact that it is primarily due to a deficiency and not to other unrecognized factors are: (1) its gradual development as the deficiency progresses; (2) the hyperplastic appearance of the marrow with "maturation arrest," quite typical of a deficiency state; (3) the well-marked reticulocytosis (and erythrocytosis) which result when the deficient substance is added to the diet; and (4) the gradual improvement in the clinical status of the affected pigeons.

The development of anemia in pigeons on deficient diets has had some previous study. Muller[23] studied the effects of various substances during recovery from the marked anemia and inanition produced by a period of complete starvation for 7 to 13 days. A mixed grain diet and broiled beef muscle contained elements which allowed complete recovery. The use of broiled beef liver, after an initial recovery of the red cell and hemoglobin levels was associated with an exacerbation of anemia, and later anorexia and marked weight loss. Liver after water extraction was without effect on the anemia of starvation, but liver after dilute alcohol extraction caused a complete remission. Muller ascribed this to the removal of some inhibiting factor present in liver, although it is possible that the lack of effect after water extraction might have been due to the loss of various factors of the B_2 complex present in liver and soluble in water.

Barlow,[2] also using the starvation technique, found that grain

and beef muscle caused improvement of anemia in most cases. Cooked or raw beef liver were without effect; however, when beef muscle and beef liver were both given, the anemia improved. Barlow also found that a diet of polished rice or a synthetic diet deficient in Vitamin B factors produced an anemia. This anemia was prevented and cured by Harris's yeast extract, but not by the Lilly liver extract 343 (Fraction G of Cohn). He attributed the ineffectiveness of liver to its deficiency in certain factors of the B vitamin.

Hogan, Richardson, and Johnson,[15] after producing beri-beri in pigeons by a deficient diet, gave large doses of concentrated Vitamin B_1. Within 1 week, recovery from polyneuritis had occurred, but a severe anemia was present with a red cell level below one million. This anemia yielded to a low calorie diet adequate in vitamins, but did not respond to flavin or the anti-dermatitis principle(s).

The anemias produced by Muller and Barlow are hardly comparable with the type produced in our experiments. The rapid onset of the anemia and the marked inanition are indicative of multiple deficiencies. In Barlow's experiments with a diet of polished rice without added B_1 the lack of the latter factor might well have led to changes in the gastro-intestinal tract, the liver, and the bone-marrow long before the changes due to deficiency in the B_2 complex could occur. The work of Hogan *et al.* is somewhat more similar to our own, but here again the preliminary depletion of B_1 might conceivably promote changes initiating the rapid onset of anemia.

C. *Anemias With B_2 Complex Deficiency in Other Species Than Pigeon.* It is hazardous to compare deficiencies of one species with those of another. In the first place, deficiencies of one fraction of B_2 complex may produce pathologic changes in one species and not in another; *e. g.*, rats do not require nicotinic acid,[5] the lack of which produces black tongue in dogs and pellagra in man. In more closely related species this is also true. Lack of riboflavin does not produce dermatitis in chickens but does so in turkeys.[18b] In the second place, the same symptom in different species may be due to deprivation of different factors in the B_2 complex. Thus, rat dermatitis is cured by B_6, a fraction of yeast which is absorbed by fuller's earth, whereas chick dermatitis is not affected by B_6 but is relieved by "filtrate factor," the filtrate resulting from removal of the above adsorbate. Finally, the diets described have differed in other particulars besides those of the known vitamins. For example, lack of certain fatty acids will cause rat dermatitis despite the presence of B_6.[4]

Anemia from a deficiency in various fractions of the B vitamin has been described in dogs, monkeys, swine, rats, and chickens.

Dogs. Miller and Rhoads[21] fed a pellagra-producing diet (deficient in Goldberger's P-P factor but not in B_6) and obtained a macrocytic anemia with megaloblastic bone-marrow. There was no improvement with liver extract; but complete recovery occurred with beef.

Spies,[27] with a similar diet, produced anemia which was prevented by ventriculin and cured with yeast.

Birch, György, and Harris[5] produced anemia with a diet containing B_6, but not P-P or lactoflavin. This anemia responded to fish (which has no lactoflavin) and to the Lilly liver extract 343 (which has no B_6), *i. e.*, the anemia was due to some other factor of the B_2 complex.

Fouts *et al.*[13] fed puppies a diet deficient in B_6 but containing casein, B_1, riboflavin, and filtrate factor. The anemia which developed responded by a reticulocyte crisis and increase in red cell and hemoglobin levels to purified, and later, crystalline vitamin B_6.

Monkeys. Day *et al.*,[8] using a modified Goldberger diet, produced anemia which was prevented by brewer's yeast.

Wills *et al.*,[33] using a similar diet, produced anemia which responded to "marmite" and liver extract. Liver extract was divided into two factors, one soluble in $(NH_4)_2SO_4$, and the other insoluble. The soluble fraction was usually effective in both pernicious anemia and the deficiency anemia in monkeys, although an occasional monkey required both fractions. The insoluble fraction was effective in pernicious anemia but without effect in monkey anemia. This anti-anemia factor for monkeys was present in yeast, marmite, and wheat germ. They make the statement, although they give no evidence, that this factor is neither B_6 nor the filtrate factor.

Rats. Sure, Kik, and Smith[29] fed rats a diet deficient in the vitamin B complex plus 500 mg. (daily) of rice polishings irradiated for 10 hours to destroy vitamin G. Some animals tended to less weight, while others developed a dermatitis. There was a much higher correlation of anemia with dermatitis than with weight loss.

Guha and Mapson[14] produced anemia on a basal diet supplemented by B_1. Autoclaved liver extract, as well as autoclaved marmite, corrected this.

Manville and Grondahl[19] placed their animals on a basal B free diet supplemented with varying amounts of yeast. After anemia developed, the animals were placed in a low pressure chamber. They found that with the higher percentages of yeast, the low pressure had a greater effect in stimulating the bone-marrow. Apparently some factor in yeast was necessary for the development of "megaloblasts" to normoblasts.

Bethell and Sturgis,[3] using a milk diet, produced a macrocytic anemia which responded to vitamin B_1. This article is published in abstract form and further details are lacking.

Swine. Miller and Rhoads[21] produced anemia in swine on a dog black tongue diet. Some of the animals developed a macrocytic type of anemia while others developed a microcytic form. The bone-marrow was hyperplastic and megaloblastic. Both types of anemia responded to Lilly's liver extract 343 (Fraction G). Control animals on Vegex or egg white developed no symptoms except achlorhydria. Egg white is deficient in both B_6 and in the anti-chick dermatitis factor (F. F.).

Chickens. With chickens fed on the Koehn-Elvehjem diet, Birch, György, and Harris[5] believed that these animals became anemic "as judged by the striking pale condition of their combs." When the maize, middlings, and extracted caseinogen were not heated, anemia did not develop. Yeast was ineffective in preventing the anemia.

Comment. Although these investigations with deficient diets in various animals present certain discrepancies and inconsistencies, in general they show the same trend. The inconsistencies are in all probability due, not only to species variations, but to the difficulties inherent in preparing exactly comparable diets. Furthermore, until very recently, the various factors had not been available in

sufficiently pure form to make one certain of the nature of the specific agent responsible for a therapeutic result. The situation in regard to recognition and purification of the various factors of the B_2 complex shows such rapid change that a publication of even a year ago is by now outdated. In the last 2 years alone, nicotinic acid has been recognized as the P-P factor, vitamin B_6 has been isolated in crystalline form, and the chick anti-dermatitis factor of Elvehjem has been stated to be pantothenic acid.[35] Although experimentation is naturally rendered more exact by the use of pure substances, certain complexities are, however, introduced because of the possibility that *combinations of pure substances* may be necessary for a given effect. Several substances are still present in the B_2 complex which (until today) have not been isolated in pure form: Vitamins B_3, B_4, B_5, W factor. Still other factors, whose physiologic effects have not even been recognized, are undoubtedly present in yeast and liver.

In the present state of our knowledge we can state quite definitely that a diet deficient in vitamin B produces a deficiency state usually accompanied with anemia in a variety of animals: pigeons, dogs, monkeys, rats, chicks, and swine. This anemia has responded in most instances to crude liver extract and to yeast. Little progress has thus far been made in elucidating which of the numerous factors in these substances is responsible for the anemia. Our investigations definitely exclude vitamin B_1, riboflavin, nicotinic acid, vitamin B_6, and in all probability the filtrate factor of Lepkovsky. Since the anemia in our cases was not microcytic and did not respond to B_6, it must differ from the hypochromic anemia produced by Fouts *et al.* in puppies. The reticulocytosis which occurred following the injection of the purified chick anti-dermatitis principle of Elvehjem may indicate that this factor is at least partially responsible for the anemia. Isolation of another factor or co-factor must await further investigation.

The findings in the bone-marrow of hyperplasia and immaturity ("maturation arrest"), the hematological findings, and the development of a reticulocyte crisis and erythrocyte response when effective substances were given resemble those seen in the "liver extract" deficiency state of humans known as "pernicious anemia."[7] The changes in the feathers and epidermis are perhaps comparable to such clinical phenomena in pernicious anemia as greying of the hair, baldness of the tongue, and so on. These similarities may indicate a possible relationship between the experimental pigeon dermatitis and the human disease. Pernicious anemia has been amply demonstrated to be a deficiency disease. The exact type of deficiency which is present has thus far not been elucidated, although the B_2 complex may be involved. In most instances this deficiency is "conditioned," as Castle has pointed out, by a gastric abnormality. In many cases, however, an inadequate diet together with a gastrointestinal defect, is responsible for the development of the syndrome.

Some cases in which the dietary factor is outstanding will respond simply to a diet rich in protein substances and containing vitamin B in excess.[1] Wintrobe's experiments with yeast and yeast products indicate that yeast alone is frequently effective in the therapy of pernicious anemia.[34] This may indicate either (1) that Castle's enzyme is not a prerequisite for the final elaboration of "liver extract-substance;" (2) that yeast, when given in excess, contains so much "extrinsic factor" that is sufficient even with the small amount of "intrinsic factor" probably present, to initiate a response; or (3) that both yeast and liver extract contain quite similar factor(s).

Our studies, which demonstrate that both dilute liver extract and yeast concentrate are effective in pigeon B_2 complex deficiency anemia bring the problem to about the same stage. The anti-pernicious anemia principle was apparently not of itself entirely effective in our anemia. Thus, in one pigeon, although a well-marked reticulocytosis ensued with dilute liver extract, no rise in erythrocytes occurred until yeast was given. In several other pigeons, highly concentrated liver extracts, containing presumably anti-P.A. principle in excess, and with but little vitamin B complex, caused a slow, rather ineffective response as compared with that of yeast. For these reasons, it is apparent that, although pigeon dermatitis and pernicious anemia have certain points of resemblance they are probably not due to the same type of deficiency.

The various attempts to use normal pigeons as assay animals in testing liver extracts[22,30] are probably invalidated, since the results which have occurred are probably due to a factor or factors in the B_2 complex and not to the anti-P.A. principle itself. Whether the latter will eventually be shown to be one of the numerous substances present in the B_2 complex remains to be seen. At any rate, the complexities of liver extract and of yeast offer a continued challenge to investigators in chemical, biological, and clinical fields.

Summary and Conclusions. 1. Pigeons on a diet of polished rice with added vitamin B_1 (thiamin chloride) parenterally developed a deficiency state (pigeon dermatitis) characterized by: 1, loss of weight, changes in the feathers and epidermis; and, 2, progressive anemia associated with a hyperplastic, immature marrow.

2. This deficiency state did not respond to riboflavin, nicotinic acid, vitamin B_6, or filtrate factor (Lepkovsky).

3. Striking clinical and hematological responses occurred with yeast concentrate, dilute (parenteral) liver extract, and (parenteral) B_2 complex. Concentrated liver extracts gave either a partial or a delayed response. Elvehjem's purified chick-anti-dermatitis principle resulted in a definite reticulocyte response which was, however, not followed by an erythrocyte increase.

4. Pigeon dermatitis is due to a deficiency in a factor or factors in the vitamin B_2 complex. This factor does not appear to be riboflavin, nicotinic acid, or vitamin B_6. It is probably not identical with the liver-extract-principle effective in pernicious anemia.

The chick anti-dermatitis principle, either alone, or in association with some unknown factor, may be the vitamin which is responsible for the deficiency state.

5. The findings in the bone-marrow and the striking hematological responses to yeast and dilute liver extract resemble those seen in the "liver extract" deficiency state of humans (pernicious anemia). Whether this indicates a possible relationship between pigeon dermatitis and pernicious anemia is problematical. At any rate, the complexities of yeast, the B_2 complex and liver extract continue as outstanding challenges to investigators in numerous fields.

REFERENCES.

(1.) **Alsted, G.**: Am. J. Med. Sci., **197**, 741, 1939. (2.) **Barlow, O. W.**: Am. J. Physiol., **91**, 429, 1930. (3.) **Bethell, F. H.**, and **Sturgis, C. C.**: J. Clin. Invest., **14**, 721, 1935. (4.) **Birch, T. W.**: J. Biol. Chem., **124**, 775, 1938. (5.) **Birch, T. W.**, **György, P.**, and **Harris, L. J.**: Biochem. J., **29**, 2830, 1935. (6.) **Dameshek, W.**: Arch. Int. Med., **50**, 579, 1932. (7.) **Dameshek, W.**, and **Valentine, E. H.**: Arch. Path., **23**, 159, 1929. (8.) **Day, P. L.**, **Langston, W. C.**, and **Shukers, C. F.**: J. Nutrit., **9**, 637, 1935. (9.) **Elvehjem, C. A.**: The B-vitamins, Except B_1 and the Flavins, in Ergebn. d. Vitamin—und Hormon forschung, Leipzig, Akademische Verlagsgesellschaft M.B.H., 1938. (10.) **Elvehjem, C. A.**, and **Koehn, C. J., Jr.**: J. Biol. Chem., **108**, 709, 1935. (11.) **Elvehjem, C. A.**, **Madden, R. J.**, **Strong, F. M.**, and **Woolley, D. W.**: Ibid., **123**, 137, 1938. (12.) **Elvehjem, C. A.**, **Philipps, P. H.**, and **Hart, E. B.**: Proc. Soc. Exp. Biol. and Med., **36**, 129, 1937. (13.) **Fouts, P. J.**, **Helmer, O. M.**, **Lepkovsky, S.**, and **Jukes, T. H.**: J. Nutrit., **16**, 197, 1938. (14.) **Guha, C.**, and **Mapson, L. W.**: Biochem. J., **25**, 1674, 1931. (15.) **Hogan, A. G.**, **Richardson, L. R.**, and **Johnson, P. E.**: J. Biol. Chem., **119**, 1, 1937. (16.) **Kline, O. L.**, **Keenan, J. A.**, **Elvehjem, C. A.**, and **Hart, E. B.**: Ibid., **99**, 295, 1932–1933. (17.) **Lepkovsky, S.**: Science, **87**, 169; 1938. (18.) **Lepkovsky, S.**, and **Jukes, T. H.**: (*a*) J. Biol. Chem., **111**, 119, 1935; (*b*) J. Nutrit., **12**, 515, 1936; (*c*) J. Biol. Chem., **14**, 109, 1936. (19.) **Manville, I. A.**, and **Grondahl, J. W.**: Am. J. Physiol., **116**, 626, 1936. (20.) **Mickelson, A.**, **Waisman, H. A.**, and **Elvehjem, C. A.**: J. Biol. Chem., **124**, 313, 1938. (21.) **Miller, D. K.**, and **Rhoads, C. P.**: J. Clin. Invest., **14**, 153, 1935. (22.) **Muller, G. L.**: Arch. Path., **14**, 774, 1932. (23.) **Muller, G. L.**, and **Scarpio, A.**: Am. J. Physiol., **88**, 259, 1929. (24.) **Nittis, S.**: J. Lab. and Clin. Med., **23**, 1119, 1938. (25.) **Reader, V.**: Biochem. J., **23**, 689, 1929. (26.) **Smith, D. T.**, **Duffin, J. M.**, and **Smith, S. J.**: J. Am. Med. Assn., **109**, 2054, 1937. (27.) **Spies, T. D.**, and **Dowling, A. S.**: Am. J. Physiol., **114**, 25, 1935. (28.) **Spies, T. D.**, **Cooper, C.**, and **Blankenhorn, M. A.**: J. Am. Med. Assn., **110**, 622, 1938. (29.) **Sure, B.**, **Kik, M. C.**, and **Smith, M. E.**: Proc. Soc. Exp. Biol. and Med., **28**, 498, 1931. (30.) **Vaughan, J. M.**, **Muller, G. L.**, and **Zetzel, L.**: Brit. J. Exp. Path., **11**, 456, 1930. (31.) **Vedder, E. B.**: Beriberi, New York, William Ware & Co., 1913. (32.) **Williams, R. R.**: Chemistry of Vitamin B_1 (Thiamin), in Ergebn. d. Vitamin—und Hormon forschung, Leipzig, Akademische Verlagsgesellschaft M.B.H., 1938. (33.) **Wills, L.**, **Clutterbuck, P. W.**, and **Evans, B. D. F.**: Lancet, **1**, 311, 1937; Biochem. J., **31**, 2136, 1937. (34.) **Wintrobe, M. M.**: Am. J. Med. Sci., **197**, 286, 1939. (35.) **Woolley, D. W.**, **Waisman, H. A.**, and **Elvehjem, D. A.**: J. Am. Chem. Soc., **61**, 977, 1939.

FOCI OF INFECTION IN PSYCHIATRIC PATIENTS.

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The causal relationship of foci of infection to general systemic diseases was recognized by Benjamin Rush[5d] in 1819 in a case of arthritis which recovered after removal of dental infection. It

was not until 1912, however, that attention to foci of infection was greatly stressed, by Billings,[2a] Rosenow, Jackson and others. In 1912, Gilmer[3] raised the question of the importance of the effect of dental foci of infection—alveolar abscesses and pyorrhea—on the general health of the individual. In 1913, Billings,[2b] studying 70 cases of arthritis deformans, concluded, "Focal disease was usually located in the head. Chronic alveolar abscess and chronic sinusitis due to streptococci were an occasional cause. Most frequent was chronic streptococcic focus of faucial tonsils. Occasionally the focus may be in the prostate gland, seminal vesicles, female genitalia and probably also in a streptococcic chronic appendicitis or a circumscribed streptococcic infection anywhere." Young,[8] in the same year, states, "In conclusion, I may say that the prostate and seminal vesicles are very frequently the site of chronic inflammatory processes which often continue for years, give very few local symptoms and are the insidious cause of remote processes. This fact should bring home to all practitioners of medicine the very great importance of rectal examinations as a routine procedure."

In the ensuing years the importance of foci of infection as a cause of systemic disease has been much debated, widely studied and variously evaluated (Pemberton,[5a,c,d,6] Bierring[1]).

While there have been a great number of articles and work relating the presence of foci of infection to such systemic diseases as arthritis, there have been few studies that show the incidence of foci of infection in physically well human beings. An attempt at such a study was made by Pemberton[5b] when he studied 100 consecutive hospital admissions for foci of infection. In this series of cases foci of infection were present in 87% of the cases, a higher incidence than the same worker obtained in arthritic patients. A just criticism of this work is that these patients were not physically well, and hence one might expect a higher incidence of foci of infection than in a group of physically normal people.

It is the purpose of the present study to determine the incidence of foci of infection in a group of patients who are apparently physically well. The group of patients we elected to study are a group of psychotic patients at this hospital who were hospitalized because of mental rather than physical sickness. There is no reason to expect in a group of mentally sick but apparently physically well patients any difference in incidence of foci of infection than would obtain in a similar economic and geographic group of physically normal human beings.

Patients on the psychiatric service at this hospital routinely have examinations for foci of infection, whether or not the routine physical examinations reveal or suggest the presence of a focus of infection. These routine "foci checks" usually involve nose and throat, dental, urology, gynecology, and sometimes cardiorespiratory

examinations by specialists in those fields. Further examinations, such as sinus washings, sinus Roentgen rays, electrocardiograms, chest films, and so on, are done if foci of infection are suggested by the routine checks. Since these examinations are routinely obtained, we believe the incidence of foci of infection in our group approximates the incidence in a similar economic and geographic group of physically normal humans.

TABLE 1.—FOCI OF INFECTION BY DISEASE GROUPS.

	Schizophrenic.	Manic-depress.	Menopausal.	Senile.	Paresis.	Alcoholic.	Total.
Male	43	15	0	4	47	34	143
Female	39	14	24	7	3	9	96
Total	82	29	24	11	50	43	239
Average age	27.5	39.1	42.7	66.1	43.9	42.5	38.9
Incidence of foci of infection	59%	55%	65%	80%	68%	62%	62.8%

From Table 1 we see that the incidence of foci of infection for our entire group is 62.8%, a figure slightly lower than the incidence of foci of infection Pemberton found in 1100 arthritic patients (70%),[5a,d,6] or in a group of 100 consecutive hospital admissions (87%).[5b]

Though 62.8% of our cases had foci of infection, none of them had arthritis and only 2 had rheumatic heart disease, both diseases widely thought to be caused by foci of infection. It is obvious then, since our patients with foci of infection did not develop arthritis or rheumatic heart disease, that there must be some other physical condition present in patients who do develop arthritis from foci of infection. It has been suggested that the arthritic patient is allergic to the bacteria present in his focus of infection or that he has a constitutional predisposition to joint involvement. Pemberton and Pierce[6] found hereditary influences in 58% of 1100 arthritic patients, and later Pemberton states,[5d] "The proverbial relation of soil and seed is here exemplified, the soil being afforded by the constitutional background, the almost necessary predisposing cause; the seed being represented by infection or some other factor, the frequently exciting agent."

There is a lower incidence of focal infection in our series than in a group of 100 consecutive hospital admissions which were evidently admitted to the hospital because of physical ailments (cardiorespiratory conditions, nephritis, arthritis, and so on. We believe that one can, of course, expect a higher incidence of foci of infection in the physically ill patient. From the above table it is also evident that there is little difference in incidence of foci of infection by disease group or by the age of each disease group.

TABLE 2.—FOCI OF INFECTION BY NUMBER OF FOCI EXAMINATIONS.

Number of foci checks.	Number of patients.	% having one focus of infection.	% having more than one focus of infection.
None	23	0	0
One	14	40	0
Two	42	40	14
Three	89	68	19
Four	71	75	37
	239		

From Table 2 we see that the majority of our patients had a minimum of 3 foci examinations (160 out of 239), while 202 out of 239 had at least 2 foci checks. Unfortunately, the mental condition present in our type of patient made foci checks difficult or sometimes impossible. A further circumstance that made it impossible for all the patients to receive all the examinations was that some left the hospital before the studies could be completed.

Table 2 shows that with the greater number of checks the known incidence of focal infection rises—40% in the group that had 1 and 2 checks, and 75% in the group that had 4 checks. An axiom of modern medicine that this confirms is simply that the known incidence of focal infection in any group of patients is in direct proportion to the thoroughness with which the patients are examined for such foci.

It would seem probable that if our entire group had the 4 foci examinations the incidence of focal infection in our entire series would approximate 75%. This compares favorably with the incidence of focal infection (70%) Pemberton found in 1100 arthritic patients. Consequently it is evident that the incidence of focal infection is approximately the same in a group of arthritic patients as in a group of apparently physically normal patients.

TABLE 3.—FOCI OF INFECTION BY SYSTEMS.

	Nose-throat.	Dental.	Urol.	Gynec.	Cardio-resp.
Number of cases checked for foci	180	174	100	67	125
Foci present	80	65	17	15	13
Per cent of cases checked having foci present	44	37	17	22	2.4
Per cent of cases checked having other pathologic conditions present	22	29	1	21	66.8

From Table 3 we see that the most common site for a focus of infection is in the nose and throat, which agrees with the early work by Billings.[2a,b] In Pemberton's[5b] study of 100 consecutive hospital admissions, he found the dental and nose and throat foci of infection to be about the same in incidence (58% and 56%). Dental foci of infection were present in a little over one-third of our patients, while two-thirds of our patients needed dental treatment. The next most common focus of infection lay in the genito-urinary tract

(22% and 17%) in our study. True foci of infection were rare in the cardiorespiratory system, being present in only 1.6% of our patients. However, such conditions as luetic heart disease, rheumatic heart disease, hypertension and arteriosclerosis, which were relatively common, were not considered foci of infection.

TABLE 4.—NATURE OF PATHOLOGIC CONDITIONS IN THE NOSE AND THROAT.

	Cases.		% of cases checked.
Foci present:			
Chronic tonsillitis—adenoids	39		22
Sinusitis	36		20
Maxillary	27	15	
Ethmoid	8	4	
Frontal	1	0.6	
Otitis media	5		3
Mastoiditis, acute rhinitis and pharyngitis	..		2 each
Atrophic rhinitis and ext. otitis	..		1 each
Laryngitis	..		0.6
Other pathologic conditions:			
Deviated septum	22		12
Tonsillar tags	7		4
Perforated septum, polypi, nerve deaf	4		2 each

From Table 4 we see that by far the two most common causes of foci of infection in the nose and throat are chronic tonsillitis and sinus infection. The diagnosis of sinus infection was based on transillumination, sinus washings, and Roentgen ray findings. Other causes of foci in the nose and throat are relatively uncommon. There are no distinctive differences in the focus of infection in the nose and throat in our different disease groups (schizophrenic, manic-depressive, and so on).

TABLE 5.—PATHOLOGIC DENTAL CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Alveolar or apical abscesses in dead, carious teeth or root fragments	53	30
Pyorrhea	27	15
Gingivitis	4	2
Other pathologic conditions:		
Caries	63	36
Dead teeth (not infected)	12	7
Calcareous deposits	4	2
Impacted molars	8	5
Cyst	1	0.5
Leukoplakia	1	0.5

From Table 5 it is clear that the most common foci of infection in the mouth are in apical or alveolar abscesses in dead, or carious teeth, or in root fragments (30%). The diagnosis of apical abscess was based on dental examinations and Roentgen rays. The next most common focus of infection in the mouth was pyorrhea (15%). It is striking that two-thirds of our patients needed dental attention of some sort, and that 36% of our group had dental caries. There are no striking differences between our different disease groups.

Urologic foci of infection were found to be present in 17% of the 100 cases examined; 16% had chronic prostatitis, 2% non-specific urethritis and 1% cryptitis. Of our paretic patients 33% had a focus of infection in the genito-urinary tract, while only 10% of all our other cases had such an infection. We believe this to be entirely logical because there is a high probability that the man who contracts syphilis will also contract a Neisserian infection with the resultant chronic prostatitis developing in later years. One patient had a malignant kidney tumor.

TABLE 6.—PATHOLOGIC GYNECOLOGIC CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Chronic cervicitis	12	18
Salpingitis	2	3
Trichomonas	1	1.5
Other conditions:		
Fibroids	3	4.5
Labial cysts	3	4.5
Rectocele and cystocele	2	3 each
Kraurosis vulvæ, polyp, pregnancy, descensus uteri, and so forth	1	1.5 each

Table 6 shows that chronic cervicitis is relatively common in women; other foci of infection are relatively uncommon.

TABLE 7.—CARDIORESPIRATORY CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Bronchitis	2	1.6
Other conditions:		
Arteriosclerosis	16	12.8
Hypertension	8	6.4
Luetic heart disease or aortitis	8	6.4
Coronary sclerosis	3	2.4
Angina and rheumatic heart disease	2 each	1.6 each
Tuberculosis	1	0.8

From Table 7 we see that the incidence of foci of infection is very low in the chest. However, other conditions are relatively common, arteriosclerosis being present in 12.8% of our cases and hypertension in 6.4%. Our incidence of luetic heart disease is undoubtedly not the normal incidence, because of the inclusion in our group of 50 paretic cases. It is noteworthy that 17% of our paretic cases, when checked by the heart specialist, Roentgen ray, and the electrocardiogram, had signs of syphilitic involvement of the heart or the aorta. Morgan[4] states that from 10 to 15% of acute untreated cases of syphilis developed cardiovascular syphilis. It is obvious, with 17% of our cases of neurosyphilis developing cardiovascular syphilis, that the development of neurosyphilis confers no immunity at all against the development of cardiovascular syphilis.

The above figure of 17% of our paretic patients developing cardiovascular syphilis certainly indicates the necessity of a careful heart

examination before any fever therapy is attempted in a paretic patient, although Stokes[7] states that the paretic patient with cardiovascular syphilis can often be carefully coaxed through two short sieges of malaria. Jauregg (quoted by Stokes) believes, however, that vascular syphilis in patients with paresis is often made worse rather than better by malaria. Be that as it may, it is certainly necessary, with the high incidence of cardiovascular syphilis in paretics, that every paretic patient have a very careful cardiovascular check before any fever therapy is attempted.

Summary and Conclusions. Two hundred and thirty-nine patients who were hospitalized because of mental rather than physical illness were studied for foci of infection. Of these cases, 62.8% had foci of infection present.

It is obvious, with the high incidence of foci of infection in physically normal patients, that every patient should have a very careful examination for foci of infection.

Since 62.8% of our group of patients had foci of infection without developing arthritis, it is evident that other conditions must be present in the arthritic patient than just a focus of infection. It has been suggested that the arthritic patient is allergic to the bacteria present or that there is some constitutional hereditary predisposition to arthritis.

The incidence of foci of infection found in any group of patients is directly proportional to the thoroughness with which such patients are examined for foci of infection.

The most common sites of foci of infection in our study were the nose and throat (44%), dental (37%), gynecologic (22%), urologic (17%), and cardiorespiratory (1.6%). The most common nose and throat infection were chronic tonsillitis and chronic sinusitis. The most common dental infections were apical abscesses and pyorrhea. The most common urologic focus of infection was chronic prostatitis, which appears to be more common in paretic patients (33%) than in other patients (10%). The most common focus of infection in the female genitalia was chronic cervicitis.

Foci of infection in the chest are rare, yet other conditions are not uncommon. Of our paretic patients, 17% had cardiovascular syphilis, a fact that indicates the necessity of examining every paretic patient very carefully for cardiovascular involvement before they are treated with fever therapy.

REFERENCES.

(1.) **Bierring, W. L.**: J. Am. Med. Assn., **111**, 1623, 1938. (2.) **Billings, F.**: (*a*) Arch. Int. Med., **9**, 484, 1912; (*b*) J. Am. Med. Assn., **61**, 819, 1913. (3.) **Gilmer, T. L.**: Arch. Int. Med., **9**, 498, 1912. (4.) **Morgan, H. J.**: J. Am. Med. Assn., **112**, 311, 1939. (5.) **Pemberton, R.**: (*a*) Arch. Int. Med., **25**, 231, 1920; (*b*) Ann. Clin. Med., **3**, 648, 1925; (*c*) Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, p. 166, 1929; (*d*) Ibid., p. 24. (6.) **Pemberton, R.**, and **Pierce, E. G.**: Am. J. Med. Sci., **173**, 31, 1927. (7.) **Stokes, J. H.**: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, p. 1182, 1936. (8.) **Young, H. H.**: J. Am. Med. Assn., **61**, 822, 1913.

ADIE'S SYNDROME.

A NON-LUETIC DISEASE SIMULATING TABES DORSALIS*

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IN 1931 W. J. Adie[1a] presented 5 cases illustrating a syndrome which was frequently diagnosed as tabes but was not tabes. This syndrome was characterized by the tonic pupil and the loss of one or more deep reflexes. These symptoms are chronic. They do not get worse or get better and they are not due to syphilis.

In 1932 Adie[1b] enlarged this syndrome to include typical and atypical types. The typical case shows an unilateral tonic pupil and one or more absent deep reflexes. These signs remain stationary, do not otherwise impair the patient's health and tend to occur in younger people, more frequently in females than in males in a ratio of about 5:1.

The atypical cases are classified: 1, tonic pupil alone; 2, atypical phases of the tonic pupil alone; 3, atypical phases of the tonic pupil with absent deep reflexes; 4, absent deep reflexes, without pupillary changes.

The typical tonic pupil may be tonic to both light and in accommodation, but most frequently is fixed to light, dilates slightly in the dark and reacts tonically in accommodation. The tonic reaction is characterized by the slow response to the stimulus usually with a latent period or delay before the response begins to take place. Moore[32a,b] states that one case showed a delay of 5 minutes before the reaction in accommodation began. The tonic pupil contracts very slowly and may eventually become smaller than the normal. When the stimulus is removed it may continue to contract (rare), may remain stationary for several seconds (the rule), or may proceed to dilate at once (common), dilation once begun tends to proceed at a rate even slower than that of the preceding contraction, and many seconds, or even minutes elapse before it regains its usual resting size.

A typical tonic pupil is larger than normal and unilateral; but it is subject to sudden variations in size, sometimes concomitantly with emotional stress. It is regular in outline. It dilates well with mydriatics and contracts with eserine. Repetition does not facili-

* Read before the American Neurological Association, June 7, 1939, at Atlantic City, N. J.

tate the movement as it does in myotonia of skeletal muscle and the tonic quality is unaffected by the administration of quinine.

An atypical tonic pupil may be bilateral. It may be smaller or of the same size as the affected pupil and may be oval in either the vertical or horizontal diameters. There may be a tonic pupil on one side and a fixed pupil on the other. Adie includes certain cases of a fixed pupil, iridoplegia or ophthalmoplegia interna in this group. Hippus has frequently been reported in association with the tonic pupil.

The loss of deep reflexes is typically confined to the ankle jerks and is most often unilateral. Adie states that the arm jerks have never* been lost in any of his patients, and that he has never seen an absent knee jerk unless the ankle jerk on the same side is also absent. Furthermore, these cases never show ataxia or sensory changes.

We are presenting 7 cases of Adie's syndrome. Moving pictures of the characteristic signs in these cases have been taken by Dr. Maurice Frocht. Stills from these moving pictures are used as illustrations in this article.

Case Abstracts. CASE 1.—A 32-year-old married white woman, had a dilated right pupil which was fixed to light but gave the typical tonic reaction in accommodation. The deep reflexes were normal.

Suddenly on September 1, 1936, this patient noticed a blurring of vision in her right eye. She consulted her physician that same day who made the note that the right pupil was dilated, fixed to light and reacted slowly in accommodation. Aside from this, her physical examination was normal. Roentgen ray examination of the sinuses and cervical spine were reported normal. The blood Wassermann reaction was negative on 3 occasions. The spinal fluid examination and the spinal Wassermann reaction were negative.

In spite of these negative findings, this patient was given a course of antiluetic therapy. In the Fall of 1937 this patient was seen by Dr. W. Guernsey Frey at the Eye Clinic at St. Luke's Hospital (No. 38279). Dr. Frey made the diagnosis of Adie's syndrome and has very kindly allowed me to include this case in this series.

The pupils in this case are typical of the Adie's syndrome. The case is atypical in that there are no reflex changes.

CASE 2. A married white woman of 28, had a dilated left pupil which did not react to light but showed the typical myotonic reaction in accommodation and an absent left ankle jerk. She also suffered from convulsive seizures, diagnosed at the Neurological Institute as idiopathic grand and petit mal.

This patient reported to the Vanderbilt Clinic (No. 544153) on March 7, 1938, because of her convulsive attacks which she had had for 12 years. She had no previous knowledge that one pupil was larger than the other and had never noticed any difficulty with vision. She entered the Neurological Institute for study March 10, 1938, and was discharged March 26, 1938, with the following diagnoses; (1) idiopathic grand and petit mal; (2) pregnancy 2 to 3 months' duration; (3) Adie's syndrome. The left pupil was larger than the right, regular in outline. It did not react to light but reacted very slowly in accommodation, eventually approximating the

* Two cases reported by Kennedy in a series of 5 were said to show absence of all deep reflexes.

right pupil in size. On ceasing to accommodate, the left pupil returned very slowly to its former size. The left pupil dilated slowly in the dark. The consensual light reflex was present from left to right, but not from right to left. One drop of 1% eserine in each eye produced a contraction of each pupil to about 1 mm. in diameter. Intramuscular injection of prostigmin increased slightly the speed of reaction of the left pupil to accomodation but did not otherwise affect it. Ten grains of quinine hydrochloride by mouth produced no change in the pupillary reaction. The left ankle jerk was absent.

FIG. 1

FIG 2

FIG. 3

FIG. 4

FIG. 1.—Case 1. The pupils at rest.
FIG. 2.—Case 1. The reaction of the left pupil to light.
FIG. 3.—Case 1. The reaction of the right pupil to light.
FIG. 4.—Case 1. The reactions of both pupils to accommodation-convergence. It took approximately 2 minutes for the left pupil to contract in accommodation and approximately 3 minutes for it to return to its resting size after the action in accommodation ceased.

Careful laboratory studies, including the blood count, analysis of the urine, blood sugar, urea-nitrogen, glucose tolerance, and spinal fluid examinations were all normal. The Wassermann reaction on the blood and spinal fluid was negative in all dilutions. Roentgen ray of the skull showed no abnormalities. The encephalogram was reported by Dr. Dyke as showing mild cerebral and cerebellar hypoplasia or atrophy. The Aschheim-Zondek test was positive.

Course.—This patient's pregnancy was normal and her child was born in October, 1938. She is still under treatment in the Vanderbilt Clinic for her convulsive disorder. The pupillary findings are unchanged and the left ankle jerk is still absent.

CASE 3.* A Puerto-Rican of 51, presented a dilated right pupil which did not react to light or in accommodation and an absent right ankle jerk.

This man was admitted to St. Luke's Hospital (No. 42001) for the first time on October 6, 1937, complaining of pains in various parts of the body. Because of language difficulty his history was difficult to obtain. He reports having had a sore on his penis in 1902 which cleared up in a few weeks with local treatment. In 1912 he first noticed that his right pupil was larger than the left. Aside from the difference in size of the pupils, he had no

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 5.—Case 2. The dilated right pupil which did not react to light but reacted tonically in accommodation.

FIG. 6.—Case 3. The dilated left pupil which did not react to light and reacted very slightly in accommodation.

FIG. 7.—Case 4. The dilated left pupil which reacted imperfectly to light and tonically in accommodation.

FIG. 8.—Case 7. The dilated right pupil which did not react to light and reacted tonically in accommodation.

symptoms at this time. In 1917 he developed a rash which was fairly generalized and itching. He was told that his Wassermann reaction was 1+ and he was given 6 injections in the vein of his arm and 10 injections in the buttocks.

The neurologic examination showed the right pupil to be large, regular and fixed to light and in accommodation. The right ankle jerk was absent. There was diminished hearing in the left ear of the middle ear type and the

* These first 3 cases were presented before the New York Neurological Society, April 5, 1939.

tonsils were enlarged and infected. Laboratory tests including analysis of the urine, blood count, blood sugar, and spinal fluid were normal. Kline and Wassermann tests were negative on both the blood and spinal fluid.

This patient's pains were thought to be due to arthritis. He was readmitted to the hospital in May, 1938, for a tonsillectomy. His blood and spinal fluid Wassermann reactions were repeated at this time and were negative. Again on a subsequent admission in February, 1939, for an attack of asthma the blood Kline test was reported negative. When last seen in May, 1939, the neurologic status was the same as reported above.

Now 51 years of age, he first noticed the enlargement of the right pupil in 1912 at the age of 24. It is unilateral and has persisted for 27 years. The right ankle jerk is absent and his serology has been repeatedly negative. In spite of the history of a 1+ Wassermann and a series of injections in 1917 we believe that this patient is an atypical case of Adie's syndrome.

CASE 4. A 40-year-old business man, showed a dilated left pupil which did not react to light and reacted tonically in accommodation. Both ankle jerks were absent and the left knee jerk could not be obtained.

In December, 1927, at the age of 27 this patient first noticed that the left pupil was larger than the right. His attention was called to this by the sudden onset of blurring of vision and an increased sensitivity of his eyes to bright lights. He was carefully examined by his family doctor at this time and in February, 1928, he was seen by Dr. George Hyslop, who made the following note: "The left pupil did not react to light and was slightly irregular. I noticed after a moment or two, the left pupil would spontaneously reduce in size. There seemed to be at times a delay in contraction to accommodation. The neurologic examination was otherwise negative save for difficulty in obtaining the knee and ankle jerks." The Wassermann reaction on the blood and spinal fluid was negative.

After 6 years observation, in 1934 the following note was made by Dr. Hyslop. "The right pupil at first was slightly larger than the left, showed a paradoxical response to direct light. The left pupil showed no reaction to light. A few moments later, in a darker room, the left pupil became larger than the right. I did not get the knee or ankle jerks."

Referred to me by Dr. Hyslop in April, 1939, he stated that after repeated assurances from Dr. Hyslop as to the benign nature of his condition he finally put the matter out of his mind. My examination was similar to that made in 1934 except that the right knee jerk was obtained. The left pupil in its resting state was larger than the right.

CASE 5. The 8-year-old son of Case 4. The father noticed that the boy's left pupil was larger than the right when he was 3 years of age. This condition has remained constant since. As the boy was perfectly well in every other respect no medical examination was made until he was brought in to see me at my request in April of this year.

The physical and neurologic examinations were entirely negative except for the anisocoria and diminished ankle jerks—right more than left. The left pupil was larger than the right. Both pupils reacted promptly to light and in accommodation and dilated promptly when the stimulation was removed. Both pupils showed a definite hippus.

While this patient does not show the typical reactions of the Adie pupil, these findings in conjunction with those of the father are highly suggestive. There is one other child in the family—a girl of 11 whose pupillary reactions and deep reflexes are entirely normal.

CASE 6. A 15-year-old Italian girl, showed a dilated left pupil which reacted imperfectly to light and tonically in accommodation. Both ankle jerks were absent and the knee jerks were obtained only on reinforcement. She also had suffered from arrested pulmonary tuberculosis.

This patient was admitted to St. Luke's Clinic (No. 8582) in November,

1937, with pulmonary symptoms dating back to July of that year. A diagnosis of pulmonary tuberculosis was made and an artificial pneumothorax was produced on the left side. She then spent several months in different sanitaria. The inequality of the pupils and absent ankle jerks were first noticed in July, 1938, and she was returned to St. Luke's hospital in August, 1938, for study. Her Wassermann reactions and the blood and spinal fluid were normal. I saw the patient in consultation on September 7, 1938. At that time her left pupil was larger than the right. It reacted poorly and imperfectly to light but was subject to spontaneous variations in size. It showed the typical tonic contraction in accommodation. The knee jerks could only be obtained on reinforcement and the ankle jerks were both absent.

This patient has been seen on repeated occasions since this time, the last visit being in May, 1939. Her pulmonary condition seems to be completely arrested but the pupillary and reflex changes remain the same.

CASE 7 was a 28-year-old single woman of Italian descent showing a dilated left pupil which did not react to light but reacted tonically in accommodation. Both ankle jerks were absent and the knee jerks unequal, the left being greater than the right.

In July, 1938, this patient noticed the difference in the size of her pupils while looking in the mirror. Because of this she reported to the Private Clinic of the Neurological Institute (No. 39090) in August, 1938, and was examined by Dr. Alfred Gallinek who has kindly referred the case to me. At the time of her admission to the clinic in August, 1938, the left pupil was larger than the right. The ankle jerks were absent and the right knee jerk was diminished. The blood Wassermann reaction was negative. The spinal fluid was not examined.

When last seen by me (April, 1939) the pupillary and reflex changes were the same as described by Dr. Gallinek in August, 1938.

Differential Diagnosis. The Argyll Robertson pupil is usually bilateral. The pupils are small and irregular. They do not react to light, react promptly in accommodation and dilate promptly once the effort at accommodation ceases. They react imperfectly and slowly to mydriatics. With the exception of the lack of response to light, these characteristics are diametrically opposed to those of the tonic pupil.

Another and to my mind very important characteristic of the Argyll Robertson pupil which differentiates it from other forms has been pointed out by McGrath[30] and that is atrophy of the iris which gives to the syphilitic eye that peculiarity so often noted by older clinicians.

Diphtheria occasionally gives rise to an ophthalmoplegia interna, but never a tonic pupil. The pupillary changes following diphtheria appear about 10 weeks after the onset of the disease, are bilateral and get completely well in a month or two.

True tonic pupils have never been reported as due to epidemic encephalitis* and no case of Adie's syndrome *per se* has ever shown any of the early or late symptoms of this disease.

The possibility of the tonic phenomenon being related to myo-

* Jaensch's case showed pallor of the optic discs and enlargement of the blind spots which automatically removes it from the Adie group, as the optic nerve must be intact in the Adie syndrome.

tonia congenita, Thomsen's disease, is one to be reckoned with. However, the absence of myotonic phenomena in skeletal muscles in all of these cases, the fact that repetition does not tend to quicken the reaction of the pupil, and that quinine has no effect upon it, makes this association seem unlikely.

Anisocoria, such as is shown in Case 5, is said to exist frequently in children and in 10% of all normal cases (Fuchs[18]). It may be produced by glaucoma, iritis, refractive errors, or the instillation of some drug. Also it may be observed in intracranial tumors, head injuries, intracranial hemorrhage, meningitis, either central or spinal and those conditions associated with Horner's syndrome. Morax[33] has reported a case of sudden dilatation of one pupil without any other demonstrable ocular or nervous system lesion. Byrne[8] lists the causes of anisocoria as follows: (*a*) reflex dilatation, (*b*) inherent dilator tonus, (*c*) chemical dilator tonus, (*d*) reflex constriction, (*e*) inherent constrictor tonus, (*f*) chemical effector constrictor tonus.

It is plain to be seen that not all cases of anisocoria fall into the group of the Adie syndrome. In the absence of demonstrable ocular and nervous system lesions, especially if there is any familial or hereditary incidence and the inequality of the pupil is associated with diminished or lost ankle jerks, one is justified in placing the case in this group.

The inclusion by Adie of the fixed pupil as an atypical form of this syndrome in confusing inasmuch as the fixed pupil is undoubtedly part of many diseases of the nervous system other than the one Adie describes. Within the limits set by Adie in his original description, namely, an unilateral fixed pupil of long standing in a young person, probably a female with or without loss of deep reflexes, but without other neurological signs, this differential diagnosis can and should be made.

Etiology. Both the localization of the lesion and the nature of it are still unknown. So far as I know, no autopsy findings on a case of Adie's syndrome have been published. Adie's statement that the tonic pupil is never caused by syphilis has been challenged by the French school and 3 cases of tonic pupil allegedly due to syphilis have been reported by L'hermitte,[29] Harvier[20] and Laignel-Lavastine.[28] In L'hermitte's case the Wassermann reaction was reported as doubtful and in the latter 2 cases the serological reactions were negative. It can be fairly stated that so far syphilis has not been established as the cause of the tonic pupil. Diphtheria and epidemic encephalitis seem definitely to be ruled out.

While this syndrome is associated with other diseases such as epilepsy, arthritis, asthma and pulmonary tuberculosis, in my series, and with influenza, encephalitis, alcoholic polyneuritis, dysthyroid states, various sympathetic disorders, psychopathic states and per-

nicious anemia as cited by Jelliffe*[25] there is a certain uniform similarity to these cases which I hope that I have illustrated in the accompanying photographs and which is even more forcibly borne in upon one in reviewing the literature. I am therefore inclined to agree with Adie that this is a benign disease *sui generis* and that this syndrome co-exists with the other diseases such as those mentioned above but is not caused by them.

In discussing the etiology from a theoretical standpoint three distinct phenomena must be accounted for. 1, The unilateral dilated pupil which reacts to mydriatics and eserine but not to light. 2, The tonic contraction of the pupil to accommodation—convergence. 3, The absence of ankle jerks and sometimes knee jerks. Under the first category we are obviously dealing with the paralysis of the pupilloconstrictor fibers of the pupil in response to light. These fibers are under the control of the parasympathetic system. The pupillodilator mechanism (sympathetic) is intact. According to Byrne[8] a lesion in the efferent tract is apt to give an unilateral change in the pupil while an afferent lesion is apt to give bilateral changes. Ranson[41] has demonstrated a small tract in the pretectal region between the posterior commissure and the oculomotor nuclei the stimulation of which causes marked constriction of the homolateral pupil and weak dilation of the contralateral pupil. It is conceivable that a paralysis or interruption of this tract would cause the reverse. Phenomenon No. 2 is even more difficult as it requires the existence of a lesion that will alter the tonus of the constrictor muscles of the pupil and ciliary body of one eye only and in a way usually associated with excess secretion of acetylcholine and stimulation of the parasympathetic system which is indeed a paradox. To explain Phenomenon No. 3 one must postulate a lesion which will alter the tonus of the lower extremities in such a way as to abolish the ankle jerk on one or both sides and sometimes the knee jerks. A peculiarly selective lesion in the pretectal region might conceivably account for all of these phenomena but the nature of the lesion is still an enigma.

Dressler[13a,b] reported the existence of this syndrome in 3 sisters of whose family history he made a careful study. Other cases existed in the families of both the mother and the father and there were several members of the family on both sides who exhibited the phenomenon of Hippus either alone or in association with the tonic pupil. On the basis of this family, Dressler believes that Adie's syndrome is an hereditary disease and that the inherited trait is a recessive one.

* A careful review of the cases referred to by Jelliffe shows them to be a conglomerate group of different types of pupillary disturbances varying from Horner's syndrome to the neurotonic pupil of Westphal. Whereas a tonic pupillary response is described as a transient phase of Wernicke's polioencephalitis superior and other midbrain and hypothalamic lesions, no chronic and enduring pupillary and reflex changes such as Adie describes has ever been shown to result from any of these diseases.

Foster Moore reports a case of a man of 70 who had had a dilated tonic pupil for 40 years, whose sister and grand-daughter were similarly affected. Rudolf[46] reports the existence of this syndrome in mother and daughter. Reese, discussing this paper, referred to a family in which 2 members had Adie's syndrome and other members of the family had Huntington's chorea. In my own series I have examined as many of the relatives of these patients as could be located and except for the father and son reported as Cases 4 and 5, there was no familial or hereditary incidence in this group of cases.

Incidence. Aside from Adie's three papers on this subject, published in 1931 and 1932, I have collected 50 additional articles on the subject through the year 1938. The 7 cases in this series have been collected in the last 18 months. This therefore is not a rare disease and I believe it is still frequently overlooked and that many of these cases are still being treated for syphilis in spite of negative serological reactions.

Summary. Seven cases of Adie's syndrome are presented and the various theories of the location and nature of the pathology of this condition are discussed. Still lacking definite proof, the facts so far elicited make the following statement tenable. Adie's syndrome is a disease *sui generis*. It runs a chronic and benign course and may exist either alone or in conjunction with other diseases. It is perhaps heredodegenerative in nature, but it is not syphilitic.

REFERENCES.

(1.) **Adie, W. J.**: (*a*) Brit. Med. J., **1**, 928, 1931; (*b*) Brain, **55**, 98, 1932; (*c*) Brit. J. Ophth., **16**, 449, 1932. (2.) **Barré, J. A.**, and **Helle**: Rev. neurol., **1**, 542, 1934. (3.) **Barré, J. A.**, and **Klein, M.**: Ibid., p. 590. (4.) **Bergmark, G.**: Nord. med. Tid-skr., **14**, 1169, 1937. (5.) **Bramwell, E.**: Trans. Med.-Chir. Soc., Edinburgh, p. 83, 1935–1936. (6.) **Bromberg, W.**: Arch. Neurol. and Psych., **33**, 676, 1935. (7.) **Brouwer, B.**: Nederl. Tijdschr. v. Geneesk., **77**, 4880, 1933. (8.) **Byrne, J. G.**: Clinical Studies on the Physiology of the Eye, London, H. K. Lewis & Co., Ltd., 1934. (9.) **Cardona, F.**: Riv. d. pat. nerv., **48**, 188, 1936. (10.) **Chavany, J. A.**: Presse méd., **43**, 1243, 1935. (11.) **Coppez, H.**: Bull. Soc. belge. d'ophth., **70**, 60, 1935. (12.) **de Busscher, J.**: J. belge de neurol. et de psychiat., **35**, 331, 1935. (13.) **Dressler, M.**: (*a*) Klin. Wchnschr., **16**, 1013, 1937; (*b*) Helvet. med. acta, **4**, 864, 1937. (14.) **Dressler, M.**, and **Wagner, H.**: (*a*) Schweiz. Arch. Neurol. u. Psychiat., **39**, 246, 1937; (*b*) Ibid., **40**, 50, 1937. (15.) **Fracasti, T.**, and **Marelli, F.**: Rev. argent. de neurol. y psiquiat., **2**, 292, 1936. (16.) **Frankel, F.**: Gaz. d. hôp., **108**, 1665, 1935. (17.) **Frogé** and **Chiniara, J.**: Bull. Soc. d'ophth. de Paris, 557–560, 1936. (18.) **Fuchs, E.**: Textbook of Ophthalmology, English trans. by A. Duane, New York, D. Appleton & Co., 1893. (19.) **Hartmann, E.**, and **Monier-Vinard, R.**: Rev. neurol., **67**, 68, 1937. (20.) **Harvier, P.**, and **Boudin, G.**: Paris méd., **1**, 177, 1935. (21.) **Hassin, G. B.**, and **Thompson, J. J.**: J. Nerv. and Ment. Dis., **80**, 430, 1934. (22.) **Holmes, G.**: Trans. Ophth. Soc. United Kingdom, **51**, 209, 1932. (23.) **Hubin, R.**: Liège. méd., **29**, 605, 1936. (24.) **Jaensch, P. A.**: Klin. Monats. f. Augenheilk., IX, XIII, 390, 1924. (25.) **Jelliffe, S. E.**: New York State J. Med., **31**, 363, 1931; J. Neurol. and Psychopath., **13**, 349, 1933. (26.) **Kennedy, F.**, **Wortis, H.**, **Reichard, J. D.**, and **Fair, B. D.**: Arch. Ophth., **19**, 68, 1938. (27.) **Kurzes**: Handbuch der Ophthalmologie, Berlin, Julius Springer, **6**, 126, 1931. (28.) **Laignel-Lavastine, H.**, **Gallot, M.**, and **Novaille, J.**: Bull. et mém. Soc. méd. d. hôp. de Paris, **53**, 351, 1937. (29.) **L'hermitte, J.**: Rev. neurol., **67**, 210, 1937. (30.) **McGath, W. M.**: J. Ment. Sci., **78**, 362, 1932. (31.) **Merritt, H. H.**, and **Moore, M.**: Arch. Neurol. and Psychiat., **30**, 357, 1933. (32.) **Moore, R. F.**: (*a*) Trans. Ophth.

Soc. United Kingdom, **44**, 38, 1924; (*b*) Ibid., **51**, 203, 1932. (**33.**) **Morax, U.**: Précis d'Ophthalmologie, Paris, Masson et Cie, 1931. (**34.**) **Muller, H. K.**: Ztschr. f. Augenh., **88**, 20, 1935. (**35.**) **Nayrac, F.**: Echo méd. du nord., **9**, 131, 1938. (**36.**) **Parker, S., Schilder, P., and Wortis, H.**: Arch. Neurol. and Psychiat., **38**, 1112, 1938. (**37.**) **Pasquatini, R., and Bollati, E.**: Note e riv. di psichiat., **67**, 205, 1938. (**38.**) **Petit, J.**: Helvet. med. acta., **3**, 238, 1936. (**39.**) **Petit, G., and Delmond, J.**: (*a*) Ann. méd. psychol., Pt. 1, **94**, 106, 1936; (*b*) Ibid., p. 236; (*c*) Ibid., p. 497. (**40.**) **Porot, A.**: Rev. neurol., **69**, 258, 1931. (**41.**) **Ranson, S. W., and Magown, H. W.**: Arch. Neurol. and Psychiat., **30**, 1193, 1933. (**42.**) **Rea, R. L.**: Neuro-ophthalmology, London, William Heinemann, Ltd., 1938. (**43.**) **Romberg, E. H.**: Ztschr. f. d. ges. Neurol. u. Psychiat., **158**, 145, 1937. (**44.**) **Romberg, E. H., and Schaltenbrand, G.**: Deutsch. med. Wchnschr., **63**, 1517, 1937. (**45.**) **Rost, J.**: Monatschr. f. Psychiat. u. Neurol., **97**, 187, 1937. (**46.**) **Rudolf, G. de M.**: J. Neurol. and Psychopath., **16**, 367, 1936. (**47.**) **Sala, G.**: Riv. san. siciliana, **25**, 780, 1937. (**48.**) **Schneider, M.**: Med. J. Australia, **1**, 153, 1933. (**49.**) **Šercl, M.**: Casop. lék. česk., **77**, 462, 1938. (**50.**) **Subirana, A.**: Arch. de neurolbiol., **15**, 93, 1935. (**51.**) **Terrasse, J., and Kipfer, M.**: Gaz. méd. de france, **44**, 385, 1937. (**52.**) **Thomas, A., and de Ajuriaguerra, J.**: Rev. neurol., **66**, 78, 1936. (**53.**) **Vampré, E.**: Arquivos do instituto Penido Burnier, **4**, 162, 1936. (**54.**) **Weber, F. P.**: Proc. Roy. Soc. Med., **26**, 530, 1933.

INTERPRETATION OF THE GLUCOSE TOLERANCE TEST.

THE NECESSITY OF A STANDARD PREPARATORY DIET.*

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IT has long been known that starvation or restriction of carbohydrate in the diet of animals or man results in a marked decrease in the ability to utilize carbohydrate. Ingestion of a test dose of glucose, under these conditions, produces hyperglycemia, glycosuria and a marked delay in clearing the blood of absorbed glucose. Although most investigators are fully aware of this phenomenon, the knowledge has not been applied in clinical medicine.

The purpose of this report is to emphasize how much the composition of the previous diet may affect the glucose tolerance test and its interpretation. Since, in mild or questionable cases of diabetes mellitus or in the differential diagnosis between non-diabetic and diabetic glycosurias, the glucose tolerance test becomes of major diagnostic importance, one must eliminate any influence which the previous dietary may have had upon the result.

In 1889, Hofmeister[10] found that if he gave a carbohydrate meal to normal dogs that had been starving previously, glycosuria resulted. This phenomenon he called "hunger diabetes." Since that time a number of investigators, working with several species of animals and also with humans, have confirmed and elaborated these findings. Bang,[1] Staub,[14] Goldblatt,[7] du Vigneaud and Karr,[6] and others have all found hyperglycemia, glycosuria and delayed removal of glucose

* The expense of this study was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.

from the blood stream, when carbohydrate was fed after a period of starvation. Furthermore, it has been shown by Southwood,[13] Greenwald *et al.*,[8] Sweeney,[15] Malmros,[11] and Tolstoi[17] that diets low in carbohydrate lead to the same type of response following ingestion of a test carbohydrate meal.

Dann and Chambers[4a] observed that a few days of carbohydrate feeding were sufficient to restore to normal the decreased utilization of carbohydrate induced by prolonged starvation. Sweeney[16] demonstrated that a single preliminary dose of glucose did not succeed in counteracting the effects of an abnormal antecedent diet.

A discussion of the mechanisms by which carbohydrate tolerance is lowered during starvation or under conditions of low carbohydrate intake is beyond the purpose of this paper. Much excellent work, however, dealing with this question, has been reported by Dann and Chambers[3,4b,c] and more recently by Haist, Ridout and Best.[9] Suffice it to say that this factor as a depressing influence upon carbohydrate utilization can be completely eliminated by a relatively short period of high carbohydrate feeding.

We have encountered a sufficient number of patients (referred to our clinic for treatment of diabetes mellitus) whose diminished tolerance for carbohydrate was based upon a deficient intake of carbohydrate, to make us realize the importance of this factor in clinical medicine.

Experimental Procedures. Early in this work we observed that the presence of undernutrition *per se* was important in determining the degree to which carbohydrate tolerance would be diminished by restriction of carbohydrate in the diet. We, therefore, chose as subjects for study 3 malnourished but otherwise normal patients, 3 normally nourished men (medical students) and 3 normally nourished women (dietitians). All 9 subjects were between the ages of 19 and 25. All were fed a standard preparatory diet (300 gm. CHO, 80 gm. P and 3000 cal.) for 3 days before the initial glucose tolerance test was done.* All gave the normal response. They were then fed a diet containing 20 gm. of carbohydrate, 50 gm. of protein and 1600 calories for 5 days following which the glucose tolerance test was repeated. Thus, the effect upon normal carbohydrate tolerance of a short period of sharp carbohydrate restriction was observed.

In addition, data are included on 3 patients wrongly diagnosed as diabetics. In these, the effect upon diminished carbohydrate tolerance of a short period of normal carbohydrate intake was observed.

Results. Table 1 shows the effects of different diets for short periods of time upon carbohydrate tolerance in normal and undernourished young men and women. A remarkable delay in clearing

* Glucose (1.75 gm. per kg. of body weight) given orally in the postabsorptive state was used as the test dose. Blood sugar was done by the Benedict method.[2]

the blood of absorbed glucose is produced in normally nourished people by a 5-day period of dietary restriction. Qualitatively the response is the same in the undernourished individuals. The degree of response to the same restriction, however, is much greater in the undernourished group. Since, initially, both groups responded to 3 days of normal dietary by giving a normal glucose tolerance curve, it must be concluded that the existence of undernutrition makes the individual more susceptible to short periods of carbohydrate restriction. Chart 1 shows the composite response of each group to high and low carbohydrate preparation.*

TABLE 1.—EFFECT OF ANTECEDENT DIETARY CARBOHYDRATE UPON GLUCOSE TOLERANCE TEST.

					Previous diet—3 days: 300 CHO, 80 P, 3000 cals. Blood sugar, mg. per 100 cc.					Previous diet—5 days: 20 CHO, 50 P, 1600 cals. Blood sugar, mg. per 100 cc.				
Sex.	Age.	Ht., in.	Wt., lbs.	Under-weight, %	F.	1 hr.	2 hr.	3 hr.	4 hr.	F.	1 hr.	2 hr.	3 hr.	4 hr.
Normal Young Men and Women.														
M	24	70	151	2	77	65	74	58	58	58	195	116	93	61
M	24	69	163	0	78	81	62	58	58	68	202	124	65	64
M	25	68	152	0	77	67	75	44	68	73	198	105	40	75
F	24	63	121	0	82	91	70	80	72	69	178	137	111	61
F	21	61	121	0	71	83	71	67	70	57	154	174	91	54
F	23	68	147	0	80	138	80	56	62	65	221	149	129	48
			Average:		77	84	74	60	67	65	191	134	88	61
Undernourished Young Men and Women.														
M	25	72	142	16	64	122	105	45	48	44	214	242	126	76
M	25	72	138	17	78	182	115	44	..	67	250	188	53	
F	19	62	103	14	75	96	72	60	68	64	244	250	182	89
			Average:		72	133	97	50	58	58	236	227	120	83

The additional 3 cases which we have chosen as examples indicate how an erroneous diagnosis of diabetes mellitus can be made, when the important factor of previous carbohydrate restriction is neglected. The first patient had been diagnosed and treated for diabetes with diet and insulin before coming to the University Hospital. The second had been considered to have mild diabetes and the third was said to have had diabetes for 20 years.†

Case Reports. CASE 1.—M. R., 5 feet 4 inches tall, a 21-year-old, white, married woman, was admitted to the University Hospital on Jan. 10, 1937, with a chief complaint of severe headaches. Marital difficulties accounted for an anxiety state. She had lost all desire for food and the weight had fallen from 115 to 94 pounds in 6 months. One month before admission glycosuria was found while she was under treatment in another hospital. A diet restricted in carbohydrate was given and 2 doses of insulin injected daily.

On admission to this hospital glycosuria was found again. Except for malnutrition the physical examination showed no abnormalities. A glucose tolerance test was done without consideration of the previous diet. The result was as follows: Fasting 83 mg. per 100 cc.; 1 hour, 238; 2 hours, 198;

* It seems worth remarking that carbohydrate restriction produced in the females of both groups a greater loss of carbohydrate tolerance than it did in the males.

† Case histories have been condensed to conserve space.

3 hours, 182. Sugar was found in all specimens of urine after ingestion of the glucose. The patient was then referred to the diabetic clinic for treatment.

In order to rule out the factor of previous carbohydrate restriction we fed her the standard preparatory diet for a period of 2 weeks during which time she gained 3 pounds in weight. The glucose tolerance test was repeated and resulted in a normal response (Chart 2). A low carbohydrate diet (20 gm. CHO, 50 gm. P, 1600 cal.) was then given for 7 days. She lost 4 pounds. It is seen from the chart that the curve rose even higher than that obtained on admission. Again the normal diet for 7 days associated with a gain of 5 pounds brought the response to normal.

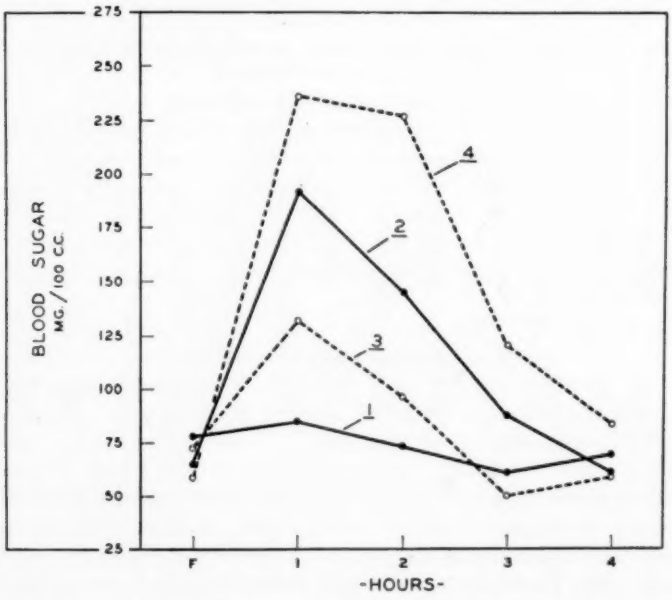

CHART 1.—Effect of previous diet upon glucose tolerance of normal and undernourished individuals.

1.—Normals—after 3 days of 3000 cals. 300 gm. CHO, 80 gm. P.	Composite curves of 6 subjects
2.—Normals—after 5 days of 1600 cals. 20 gm. CHO, 50 gm. P.	
3.—Undernourished—after 3 days of 3000 cals. 300 gm. CHO, 80 gm. P.	Composite curves of 3 subjects
4.—Undernourished—after 5 days of 1600 cals. 20 gm. CHO, 50 gm. P.	

Comment. This case serves to emphasize how promptly and with what magnitude glucose tolerance will be affected by changes in the preparatory dietary carbohydrate in a malnourished but otherwise normal individual.

CASE 2.—A. W., male, aged 72, 5 feet 5 inches tall, weight 108 pounds, entered the University Hospital on April 13, 1938, because of bladder

calculi. A heavy glycosuria was found on routine urine examination. In the preceding 3 weeks he had lost his appetite and 6 pounds in weight. A glucose tolerance test, done without consideration of the previous dietary, was found to be: Fasting, 85 mg. per 100 cc.; 1 hour, 224; 2 hours, 212; 3 hours, 138. Glycosuria appeared in all of the urine specimens collected after the glucose ingestion. He was referred to the diabetic clinic for treatment.

He was given the standard normal diet for 8 days during which he gained 4 pounds in weight. Chart 3 shows the glucose tolerance responses after 5 days of this diet and again after 8 days.

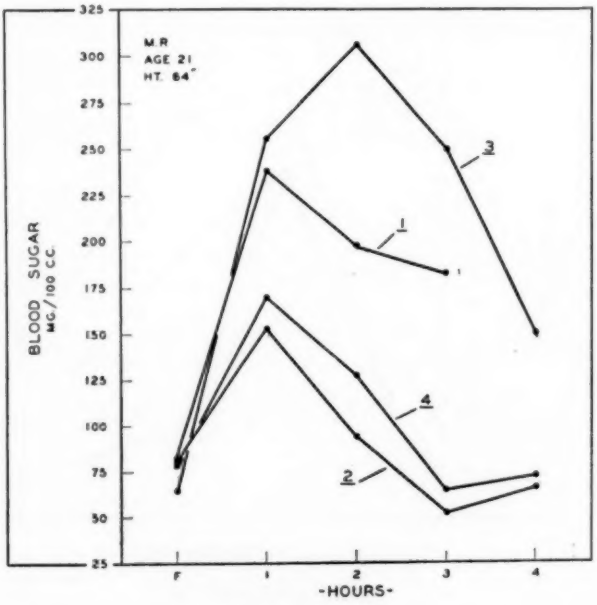

CHART 2.—Case 1.

1. Test done on admission.			Weight 94 lbs.
2. After 2 weeks	3000 cals.	300 gm. CHO, 80 gm. P.	Weight 97 lbs.
3. After 7 days	1600 cals.	20 gm. CHO, 50 gm. P.	Weight 93 lbs.
4. After 7 days	3000 cals.	300 gm. CHO, 80 gm. P.	Weight 98 lbs.

Comment. Two points are worthy of mention: (1) That following long-standing undernutrition and carbohydrate restriction, it may require more than 5 days of high carbohydrate feeding to effect complete return of normal carbohydrate tolerance. (2) The final curve, which we consider normal, reaches a peak of 184 mg. per 100 cc. in the first hour. This is higher than any of the curves on the other subjects following the preparatory diet. It has been shown, however, that normal old people exhibit a somewhat lower tolerance for carbohydrate than young people.[5,12] This probably accounts for the difference.

CASE 3.—A. O., male, aged 62, 5 feet 6 inches tall, weight 149 pounds, was first admitted to the University Hospital on Dec. 11, 1934, with a typical story of peptic ulcer. A heavy glycosuria was found in the routine urine examination. He said that he had been considered a diabetic for 20 years because sugar had been found consistently in his urine during that time. On several occasions he had been treated by mild restriction of dietary carbohydrate without affecting the glycosuria. On admission (1934) he was given a low carbohydrate diet. The glycosuria promptly cleared. After having been on this diet (20 CHO, 50 P, 1600 cals.) for 4 days a glucose tolerance test was done in order that the diagnosis be confirmed. No thought, however, was given to the fact that he had been

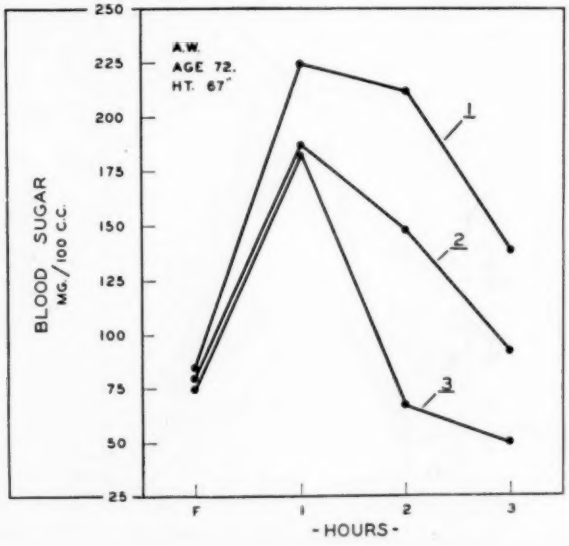

CHART 3.—Case 2.

1. Test done on admission. Weight 108 lbs.
2. After 5 days 3000 cals. 300 gm. CHO, 80 gm. P. Weight 112 lbs.
3. After 8 days 3000 cals. 300 gm. CHO, 80 gm. P. Weight 113 lbs.

prepared for the test on a low carbohydrate diet. The result was as follows: Fasting, 65 mg. per 100 cc.; 1 hour, 223; 2 hours, 218; 3 hours, 124. Glycosuria occurred in all specimens after glucose ingestion. This was considered to indicate impaired utilization of carbohydrate. The carbohydrate of the diet was gradually raised and it was found that 150 gm. of carbohydrate daily was all that could be tolerated without glycosuria. He was, therefore, discharged as a diabetic on Dec. 29, 1934, with a diet containing 150 gm. of carbohydrate and maintenance calories. He remained on this diet for over 3 years and returned on Mar. 14, 1938, for a reëxamination of his diabetic status. There had, in the interim, been intermittent glycosuria.

His weight on Mar. 14, 1938, was 148 pounds (149 on the original admission). He was given 3000 calories, 300 gm. of carbohydrate and 80 gm. of protein daily for 6 days during which time glycosuria was almost always

present. A glucose tolerance test at the conclusion of this preparatory period showed a normal curve (Chart 4) but the urine specimens during the test indicated that the renal threshold for glucose was somewhere between 90 and 112 mg. per 100 cc. He was discharged on an unrestricted diet and told that he had renal glycosuria.

Comment. This case indicates how a patient with renal glycosuria can be misdiagnosed as a diabetic when the glucose tolerance test is done after a period of carbohydrate restriction. Continuous glycosuria, because of a low renal threshold, resulted in the pre-

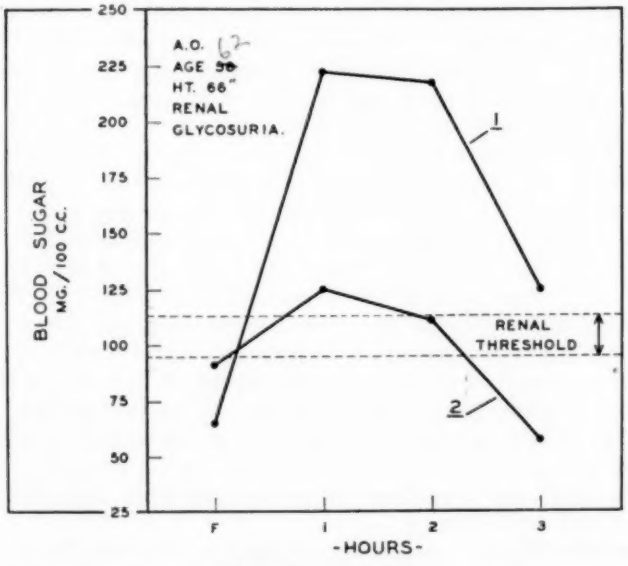

CHART 4.—Case 3.

1. After 4 days 1600 cals. 20 gm. CHO, 50 gm. P (1934). Weight 149 lbs.
2. After 5 days 1000 cals. 300 gm. CHO, 80 gm. P (1938). Weight 148 lbs.

scription of a diet limited in carbohydrate. A glucose tolerance test, under these conditions, revealed a diabetic type of response. Thus, the usual criteria for the diagnosis of diabetes mellitus were satisfied. A glucose tolerance test after adequate carbohydrate preparation, however, disclosed normal carbohydrate tolerance and renal glycosuria. In this case malnutrition was not a factor. The original abnormal response was the result of previous carbohydrate restriction.

Discussion. It has been shown repeatedly that restriction of dietary carbohydrate in the normal individual results in a significant decrease in the rate of utilization of glucose. Yet it is not customary to scrutinize the antecedent dietary of the patient before interpreting the glucose tolerance test. The experiments reported here

show again how greatly the normal rate of glucose utilization can be depressed by sharply limiting the intake of carbohydrate for several days prior to the test. In addition, it is found that when undernourished individuals, exhibiting normal carbohydrate tolerance, are subjected to the same restriction, a more marked delay in the utilization of glucose results. Examples of erroneous diagnoses of diabetes, due to failure to recognize previous restriction of dietary carbohydrate, are cited.

Claims have been made that the glucose tolerance test is a poor indicator of the ability of the organism to dispose of carbohydrate. We believe that much of the confusion arises from the lack of standardized preparatory period prior to the performance of the actual test. Much has been done to standardize the technique of doing the test, such as dosage of glucose per unit of body weight, time of obtaining blood samples, and so on. But in clinical practice, at least, the important influence of the previous dietary has been neglected. In order to obtain more standardized and comparable glucose tolerance tests we have modified the procedure by insisting that a standard preparatory diet be eaten for at least 3 days before the test is done. This diet is made up of 300 gm. of carbohydrate, 80 gm. of protein and, at least, maintenance calories. In cases in which it is known beyond question that the dietary of the preceding few days has been adequate for maintenance and abundant in carbohydrate one need not prepare the patient. When one encounters a diabetic type of glucose tolerance test with a fasting blood sugar value at or near normal, he should repeat the test after adequate dietary preparation. The objection that such a procedure entails greater effort and time does not justify errors in diagnosis due to lack of such procedure.

Diabetics who have taken the standard preparatory diet for three to five days have not been harmed in any way. The temporary increase in glycosuria disappears shortly after the test diet is discontinued.

In most cases, however, a glucose tolerance test is not necessary in order to make the diagnosis of diabetes. It is in the mild cases or in ruling out non-diabetic glycosurias that the glucose tolerance test becomes of major diagnostic importance. These are just the cases in which an erroneous diagnosis of diabetes may be made if, previous to the test, the intake of food has been limited.

The same preparatory precautions must be applied in any condition in which the glucose tolerance curve is to be used as a help in diagnosis. In hyperinsulinism, for example, the glucose tolerance curve often shows a precipitous fall to hypoglycemic levels when done after the standard preparatory diet. Restriction of dietary carbohydrate for several days before the test results in a much less marked drop of the blood sugar. Hence, under these conditions, the glucose tolerance test loses its value as a diagnostic aid.

Thus it appears evident that in order that glucose tolerance tests be in any way comparable and worthy of interpretation, they must be preceded for several days by the ingestion of an adequate diet. Our standard preparatory diet list is seen in Table 2.

TABLE 2.—STANDARD PREPARATORY DIET.

(80 gm. protein, 300 gm. carbohydrate, 2800 cals.)

Diet Plan.

Breakfast:	
Fruit	1 serving
Cereal	1 serving
Bread	2 slices
Butter	1 tablespoon
Cream	½ cup
Jelly or sugar	2 tablespoons
Beverage	
Dinner:	
Meat or substitute	1 large serving
Potato or substitute	1 serving
Cooked vegetable or Salad	1 serving
Bread	1 slice
Dessert	
Jelly or sugar	2 tablespoons
Butter	2 tablespoons
Cream	3 tablespoons
Beverage	
Supper:	
Meat or substitute	1 medium serving
Potato or substitute	1 serving
Cooked vegetable or Salad	1 serving
Bread	2 slices
Dessert	
Jelly or sugar	2 tablespoons
Butter	2 tablespoons
Beverage	

One pint of milk daily is added to the above diet plan. Coffee and tea may be taken as desired. One ounce of sugar candy may be substituted for 2 tablespoons of sugar or jelly.

Conclusions. 1. A short period of carbohydrate restriction in the normal person causes a marked delay in the rate of utilization of carbohydrate as indicated by the glucose tolerance test.

2. Undernourished individuals respond to the same procedure with a greater loss of carbohydrate tolerance.

3. Erroneous diagnoses of diabetes mellitus are made when the factor of previous carbohydrate restriction is neglected.

4. Unless the influence of previous carbohydrate restriction is removed by means of an adequate preparatory diet, the glucose tolerance test is not reliable as an indicator of the individual's ability to utilize carbohydrate.

REFERENCES.

(1.) **Bang, I.**: Der Blutzucker, Wiesbaden, J. F. Bergmann, 1913. (2.) **Benedict, S. R.**: J. Biol. Chem., **92**, 141, 1931. (3.) **Chambers, W. H.**: Physiol. Rev., **18**, 248, 1938. (4.) **Dann, M.**, and **Chambers, W. H.**: (*a*) J. Biol. Chem., **89**, 675, 1930; (*b*) Ibid., **95**, 413, 1932; (*c*) Ibid., **100**, 493, 1933. (5.) **Deren, M. D.**: J. Lab. and Clin. Med., **22**, 1138, 1937. (6.) **du Vigneaud, V.**, and **Karr, W. G.**: J. Biol. Chem., **66**, 281, 1925. (7.) **Goldblatt, M. W.**: Biochem. J., **19**, 948, 1925. (8.) **Greenwald, I., Gross, J.**, and **Samet, J.**: J. Biol. Chem., **62**, 401, 1924–25. (9.) **Haist, R. E., Ridout, J. H.**, and **Best, C. H.**: Am. J. Physiol., **126**, 518, 1939. (10.) **Hofmeister, F.**: Arch. exp. Path. u. Pharmakol., **26**, 355, 1889–90. (11.) **Malmros, H.**: Acta med. Scand. (Suppl. 27), p. 1, 1928. (12.) **Marshall, F. W.**: Quart. J. Med., **24**, 257, 1931. (13.) **Southwood, A. R.**: Med. J. Australia, **10**, 460, 1923. (14.) **Staub, H.**: Ztschr. f. klin. Med., **93**, 89, 1922. (15.) **Sweeney, J. S.**: Arch. Int. Med., **40**, 818, 1927. (16.) **Sweeney, J. S., Muirhead, J. J.**, and **Allday, L. E.**: Am. J. Clin. Path., **7**, 482, 1937. (17.) **Tolstoi, E.**: J. Biol. Chem., **83**, 747, 1929.

THE COMPOSITION OF INTRAPLEURAL AIR IN ARTIFICIAL PNEUMOTHORAX.

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Nearly 150 years ago Astley Cooper (quoted by Abernethy[1]) injected air into the pleural cavity and demonstrated that it caused no inflammation. Between 1888–1892 Forlanini (according to Hamman and Sloan[6]) instituted injection of gas into one pleural cavity as a therapeutic measure in the treatment of pulmonary tuberculosis. Interest in the composition of gas present in the pleural cavity began with John Davy.[5] His analyses did not give accurate results because they were made postmortem, when the carbon dioxide tension is greatly increased and the oxygen tension decreased. Since then many workers have been interested in this problem (see Campbell[2]). In 1932, Coryllos[4] published a preliminary report of analyses of the intrapleural air in patients with artificial pneumothorax.

In a healthy pleural cavity, no matter what the composition of the gas injected may be, the mixture resulting after equilibrium has been established (*i. e.*, after about 2 days) has the same composition,

namely, oxygen 2 to 4% and carbon dioxide 6 to 8%. In the case of artificial pneumothorax in pulmonary tuberculosis this composition is modified by variations in the degree of collapse, histologic changes in the pleura, the presence of fluid or inflammatory processes and the presence of broncho-pleural fistulæ.

The present study was undertaken in an attempt to confirm Coryllos' findings and, if possible, to apply them in the practical management of artificial pneumothorax.

After a preliminary pressure reading, a sample of intrapleural air was withdrawn into an oiled syringe, and a sample of fluid, if any was present, was obtained for bacteriologic study. Serial analyses were performed on selected cases and, whenever possible, findings were checked postmortem. Seventy-four analyses were done on 35 patients. An attempt was made to classify the results according to the type of fluid (if any) present, as Coryllos had done.* While a rough correlation was obtained, it was found that the composition of the intrapleural air, especially in cases of long-standing pneumothorax, was so modified by other factors as to limit the usefulness of such a classification. The oxygen values in particular were difficult to interpret in terms of any single factor. They showed a tendency to vary inversely with the carbon dioxide values, but there were numerous exceptions. Our failure to confirm the findings of Coryllos with respect to the sharp demarcation of his groups may have been due partly to difference in the type of patient studied. The majority of the cases which we studied were characterized by pneumothorax of long standing with either chronic or intermittent fluid. It is possible that vascular and histologic changes in the pleura may have been important modifying factors with regard to the composition of the intrapleural air.

Since the diffusibility of carbon dioxide through living membranes is 20 to 30 times as great as that of oxygen, it would, *a priori*, be expected that oxygen might fail to reach equilibrium with the surrounding tissues in those cases in which pleural permeability has been reduced by inflammatory processes. Accordingly, we have classified our results according to the percentage of carbon dioxide in the intrapleural air. In Group I, the intrapleural air contained more than 10% carbon dioxide; Group II, 8 to 10%; Group III, 6 to 8%; and Group IV, less than 6%.

Group I (28 analyses on 16 patients). Of the 16 patients in this group, all had fluid which contained tubercle bacilli. One patient had a clear fluid, 11 had frankly purulent fluid, while the other 4 had fluid which was intermittently purulent. It is significant that the composition of the intrapleural air in the cases of intermittent

* Coryllos[3] gave the following classification:
(*a*) No fluid. CO_2 = 6%. O_2 = 3 to 4%.
(*b*) Straw-colored fluid. CO_2 = 6 to 8%. O_2 = 1 to 2%.
(*c*) Purulent fluid. CO_2 = more than 8%. O_2 = less than 1%.

fluid often remained practically unchanged for weeks following complete reabsorption of the fluid, so that the presence or absence of fluid and the type of fluid cannot be the sole determining factors. For this reason, single analyses are often of little value; whenever possible serial analyses should be performed. Only in this way can the presence of small broncho-pleural fistulæ, which are intermittently sealed off by the fluid, be revealed. As an example, the case of S. G. may be considered:

CASE 1.—S. G., a 41-year-old Negress with tuberculosis of the lymph nodes and a far advanced, exudative tuberculous process involving areas throughout the right lung and the upper half of the left lung, had a right artificial pneumothorax instituted August 2, 1938. On September 21, 1938, the patient developed an acute pleurisy with effusion on the right side, and has continued to form fluid to date (June 1, 1939). Pressure readings are obtained with difficulty, but have never been suggestive of a broncho-pleural fistula. The patient has never raised pleural fluid with sputum. General condition at present (June 1, 1939) is poor.

Intrapleural air analyses. 11–9–38 $CO_2 = 10.23$, $O_2 = 3.53$. 450 cc. clear, dark fluid, positive for tubercle bacilli on concentrate smear.

11–23–38 $CO_2 = 10.12$, $O_2 = 4.34$. 300 cc. fluid, as above.

12–7–38 $CO_2 = 8.46$, $O_2 = 5.88$. 300 cc. fluid, as above.

2–10–39 $CO_2 = 6.92$, $O_2 = 7.92$. 300 cc. clear fluid, neg. T.B. on smear, pos. on culture. Analyses show trend toward fistula, but no clinical signs.

2–27–39 $CO_2 = 2.94$, $O_2 = 15.10$. Some fluid present, not aspirated. Analyses and clinical signs are now definitely indicative of fistula. Intrapleural pressures atmospheric.

5–29–39 $CO_2 = 10.47$, $O_2 = 0.22$. Fluid now purulent. Fistula has closed.

The oxygen values of the intrapleural air in Group I patients varied from 0.22 to 4.59%. The higher values were obtained in cases of intermittent fluid and of small broncho-pleural fistulæ periodically sealed off by fluid. In view of the much greater disparity between the oxygen concentration of intrapleural and alveolar air as compared with the corresponding values for carbon dioxide, and since, furthermore, oxygen is much less diffusible than carbon dioxide, it might be expected that oxygen values would vary more widely than carbon dioxide values in cases of this type. For this reason, carbon dioxide concentration is of greater significance in following the course of fluid formation and reabsorption, while the oxygen values in serial analyses reveal the presence of fistulæ intermittently closed, as well as giving some indication of the degree of impairment of permeability in thickened pleuræ.

GROUP II (10 analyses on 8 patients). All the patients in this group had fluid in the pleural cavity. Only one of these fluids was purulent, while the others were all recent effusions. It is a remarkable fact that in 5 out of the 7 cases of recent acute effusions, the oxygen concentration of the intrapleural air was 1% or less, a value which Coryllos found only in cases of purulent fluid. After

the fluid had been present for a variable length of time (1 week up to several months), the oxygen concentration rose to 2 to 3%, the value which we have found to be characteristic of clear fluids. The oxygen concentration of intrapleural air is presumably determined by two factors: the utilization of oxygen by the leukocytes and organisms present in the pleural fluid, and secondly, by the type of equilibrium established between the intrapleural air and the surrounding tissues and fluids. The latter factor has been discussed at some length by Matsuzawa[7] and Campbell.[2] Neither of these workers is able to explain the low oxygen concentration of intrapleural air after stabilization of a pneumothorax. Apparently, in the cases of recent acute effusions presented above, equilibrium between intrapleural air and the surrounding tissues and fluids was not attained until the acute symptoms attending the formation of the effusion had subsided. This is another example of the danger of depending on single analyses, particularly with reference to oxygen values, in the interpretation of fluid formation and reabsorption. Further emphasis is given to this point by the fact that the highest intrapleural oxygen value in this entire group occurred in the only case in which the pleural fluid was purulent.

GROUP III (10 analyses on 7 patients). Of the 7 patients in this group, 3 had no fluid, 3 had clear fluid, and 1 had no fluid at the time of the first analysis but developed fluid during the period in which serial analyses were performed. The average values were as follows:

(*a*) No fluid —CO_2 = 6.68, O_2 = 3.31.
(*b*) Clear fluid —CO_2 = 7.52, O_2 = 2.61.
(*c*) Fluid forming—(1) no fluid. CO_2 = 6.88, O_2 = 4.67.
(2) clear fluid present. CO_2 = 9.52, O_2 = 1.08.

GROUP IV (16 analyses on 10 patients). This group is of interest in connection with the diagnosis of broncho-pleural fistula. The average CO_2 value was 3.63% (range 0.49 to 5.49%). The average O_2 value was 12.39% (range 4.74 to 19.63%). Five of the 10 patients in this group had clinical symptoms of fistulæ, confirmed postmortem in 2 cases. The case of O. Y. is typical.

CASE 2.—O. Y., a 41-year-old white male of Slavic descent, entered Herman Kiefer Hospital on May 25, 1936, with far advanced bilateral tuberculosis. Left artificial pneumothorax was unsuccessful, but right pneumothorax was established on June 1, 1936. Purulent fluid subsequently developed in this space and was aspirated frequently until it disappeared in November, 1937. The space remained free of fluid until May 18, 1938, when a spontaneous collapse of the right lung occurred, with initial intrapleural pressure reading of +6, +11. Purulent fluid then reappeared and persisted until death on March 2, 1939. The following statement is quoted from the autopsy report:

"The right lung is completely collapsed against the medial wall. The pleural surfaces are covered with a thin, purulent exudate, smears of which

reveal acid-fast bacilli and staphylococcus albus. Below the middle of the anterior margin of the upper lobe is a deep indentation, in the base of which there is a rounded opening from which air escapes on inflation of the lung through the trachea."

Intrapleural air analyses. 6–6–38 CO_2 = 13.53, O_2 = 6.03. Small amount of thick, purulent fluid. Spontaneous pneumothorax May 18, 1938. Intrapleural pressures highly positive.

7–27–38 CO_2 = 1.70, O_2 = 19.40. 400 cc. thick purulent fluid. Pressures highly positive.

8–3–38 CO_2 = 1.68, O_2 = 19.60. 300 cc. thick, purulent fluid. Pressures remained unchanged before and after removal of 300 cc. fluid, saline irrigation and injection of 20 cc. of gomenol.

8–10–38 CO_2 = 1.21, O_2 = 19.97. 600 cc. thick, purulent fluid.

8–24–38 CO_2 = 1.34, O_2 = 19.45. 300 cc. thick, purulent fluid. Open drainage established August 31, 1938. Patient died March 2, 1939.

The other 5 cases had very similar analyses without clinical signs of fistulæ. Coryllos[3] reported similar cases in which fistulæ were found postmortem. Apparently, then, intrapleural air analyses are more reliable than are clinical symptoms in diagnosing bronchopleural fistulæ.

Discussion. The present work confirms the findings of Coryllos, without reservation, *only* with regard to the diagnosis of bronchopleural fistulæ. Even here, unless the fistula is quite large, it is likely to be intermittently closed by fluid, obscuring the changes in intrapleural air and necessitating serial analyses.

In the absence of a fistula, the CO_2 percentage of the intrapleural air is a fairly reliable index of the type of fluid present, at least during the period of formation. The case of I. S. illustrates this point:

Case 3.—I. S., a 14-year-old Negress, had bilateral pulmonary tuberculosis and severe, but easily regulated, diabetes. Intrapleural air analyses and intrapleural pressure suggested presence of broncho-pleural fistula, and for this reason, a right phrenic crush was performed on November 18, 1938. Fistula closed and 48 hours later fluid appeared for the first time and persisted until death, which occurred January 31, 1939. Postmortem examination revealed collapse of right lung and thick, purulent empyema fluid in right pleural space.

Intrapleural air analyses. 11–11–38 CO_2 = 4.58, O_2 = 13.30. Spontaneous pneumothorax on October 26, 1938. No clinical signs of fistula. No fluid present.

11–16–38 CO_2 = 6.50, O_2 = 5.17. Has clinical signs of fistula. No fluid but costal angle blurred.

11–21–38 CO_2 = 8.57, O_2 = 2.68. 300 cc. clear fluid, positive tubercle bacilli on culture. Fluid appeared November 20, 1938, following phrenic crush on November 18, 1938, which closed the fistula.

12–7–38 CO_2 = 11.18, O_2 = 4.22. 300 cc. clear fluid, which turned purulent a few days later. Patient died January 31, 1939.

When fluid is being periodically formed and reabsorbed, intrapleural air analyses may be misleading. Fluid may entirely disappear without causing an appreciable change in the composition of the air present. This is possibly to be explained by the great

thickening of the pleura often found in these patients, which results in marked decrease in permeability to gases. Residual amounts of fluid rich in leukocytes and organisms may be a contributing factor. The case of B. P. is typical:

CASE 4.—B. P., a 34-year-old Italian male, had far advanced pulmonary tuberculosis involving the upper two-thirds of each lung. Following right pneumothorax he developed fluid in the right pleural space. This fluid cleared and reappeared on several occasions. General condition has shown marked improvement.

Intrapleural air analyses. 10–26–38 CO_2 = 11.64, O_2 = 2.03. 300 cc. cloudy fluid, positive tubercle bacilli on culture.

2–24–39 CO_2 = 12.13, O_2 = 0.75. Fluid reabsorbing.
2–27–39 CO_2 = 11.95, O_2 = 0.96. No fluid present.
5–19–39 CO_2 = 11.74, O_2 = 1.97. 175 cc. clear fluid present.

The oxygen values of the intrapleural air are difficult to interpret. After stabilization of a pneumothorax, and in the absence of fluid, the oxygen tension is lower than that of any of the surrounding tissues and fluids, as was pointed out by Matsuzawa.[7] With the onset of fluid, especially if attended by acute symptoms, the oxygen tension may drop sharply, only to rise again after subsidence of the symptoms. With this exception, there seems to be a rough inverse relation between oxygen tension of the intrapleural air and purulency of the fluid. Oxygen analyses are of greatest value in following the course of broncho-pleural fistulæ, intermittently closed by fluid, because of the slow rate of reabsorption of oxygen. The reason for the initial drop in oxygen tension in cases of hot effusions is unknown.

Summary and Conclusions. An attempt has been made to confirm the findings of Coryllos, who reported a high degree of correlation between the composition of intrapleural air and the type of fluid, if any, present in the pleural cavity. The validity of the diagnosis of broncho-pleural fistulæ by means of intrapleural air analyses has been confirmed. In the absence of fistulæ, a fair degree of correlation has been found between the carbon dioxide tension of intrapleural air and the purulency of the fluid, except in cases of intermittent formation and reabsorption of fluid. The oxygen analyses have been found useful in the study of small fistulæ periodically closed by fluid, but the degree of correlation between oxygen tension of intrapleural air and purulency of fluid was rather low. In many cases single analyses of intrapleural air are likely to be misleading; serial analyses should always be performed when possible.

REFERENCES.

(1.) **Abernethy, J.**: Surgical and Physiological Essays, London, 1793. (2.) **Campbell, J. A.**: Physiol. Rev., **11**, 1, 1931. (3.) **Coryllos, P. N.**: J. Thor. Surg., **7**, 48, 1937. (4.) **Coryllos, P. N., Konterwitz, H.,** and **Levine, E. R.**: Am. Rev. Tuberc., **26**, 153, 1932. (5.) **Davy, J.**: Phil. Trans. Roy. Soc., **113**, 496, 1823. (6.) **Hamman, L.,** and **Sloan, M. L.**: Johns Hopkins Hosp. Bull., **24**, 53, 1913. (7.) **Matsuzawa, D.**: Quart. Bull. Seaview Hosp., **2**, 363, 1937.

BOOK REVIEWS AND NOTICES

THE NEUROGENIC BLADDER. By FREDERICK C. MCLELLAN, M.S., M.D., Instructor in Surgery, University of Michigan Medical School, Ann Arbor. Pp. 206; 9 illustrations and 49 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, $4.00.

IN view of the confusion in the minds of practitioners, surgeons and neurologists on the diagnosis and treatment of the neurogenic bladder, it is surprising that a monograph such as the author's was not written long ago. The author deserves praise for his efforts in gathering together the abundant though scattered literature on the subject and is to be congratulated on his success in welding it into a coherent presentation of the subject. To this task he brings his personal experience derived from the cystometric study of 500 cases.

The first half of the monograph is devoted to the nervous anatomy and physiology of the bladder and to its anatomic and physiologic relationships to the spinal and suprasegmental levels of the nervous system. Because of its theoretical interest and diagnostic implications this section will be especially attractive to neurologists and neurosurgeons. The second part of the book is given over to the clinical classification and description of the various types of bladder dysfunctions and their diagnosis by cystometry, a detailed description of the cystometric technique and a discussion of the differential diagnosis between the neurogenic bladder and the various kinds of local bladder disease. There is a short but adequate section on the treatment of the neurogenic bladder. An appendix of 49 cystometric charts is included to illustrate the text.

The monograph suffers from some faults in organization. The cystometric charts would be more valuable if they accompanied the text rather than being placed in an appendix. There is considerable reduplication of material and repetition of ideas. The style while simple at times lacks clarity in several sections, particularly those dealing with spinal and cerebral neurophysiology. The author's nihilistic attitude toward the value of the parasympathetico-mimetic drugs in treatment conflicts with current trends and the claims advanced for their efficacy. He is also pessimistic concerning the value of presacral neurectomy. In view of his large experience the author's arguments against these procedures are convincing. In spite of the prevalence of the term "neurogenic," we must protest against a barbarism which is in the same class as "the acute abdomen" and the "operated patient." Why not the equally brief and more correct term, "neuropathic bladder"?

Comforting to many readers will be his championship of the indwelling catheter in the treatment of bladder paralysis consequent to sacral cord lesions. The recent but rather general aversion to the use of this venerable instrument seems to be unfounded especially if proper precautions are taken to prevent peri-urethral infections.

The new methods of providing tidal flow are said to have certain advantages in the control of infection but the author doubts their value as a re-educator of bladder function, a claim that has been made by the inventors of the device.

A complete bibliography particularly of the English literature adds to the value of this timely and excellent monograph. I. R.

EXPERIMENTAL PHARMACOLOGY AND MATERIA MEDICA. By DENNIS E. JACKSON, PH.D., M.D., F.I.C.A., Professor of Pharmacology, Materia Medica, and Therapeutics in the University of Cincinnati, College of Medicine, etc. Pp. 906; 892 illustrations, including 55 color plates. Second edition. St. Louis: The C. V. Mosby Company, 1939. Price, $10.00.

THIS will be a valuable reference book for both students and instructors of pharmacology and physiology insofar as it represents an unusually complete collection of the various methods (many of them devised by the author) employed in animal experimentation. Operative procedures, apparatus and anatomic approaches are completely and beautifully illustrated in 892 figures, including 55 color plates. In addition there are excellent chapters on shop work, including the basic principles of glass blowing and metal work. There is also a short chapter on photography.

Since this is not a text in pharmacology but rather a laboratory manual that poses pertinent questions without answering them, it cannot be recommended to the general medical profession. As a laboratory guide, a more discriminating selection of a few fundamental experiments in connected sequence might better have served the purpose than the collection of 217 oft-repetitive exercises that the author has assembled for choice. The chapters on prescription writing and materia medica are well written and profusely illustrated. Since this book must necessarily be used in conjunction with a systematic text in pharmacology, a much smaller and more compact book might be more appropriate for student use.

J. C.

HANDBOOK OF SKIN DISEASES. By LEON HUGH WARREN, B.A., M.D., M.Sc. (MED.), Formerly Instructor in Dermatology and Syphilology at the School of Medicine, Temple University; Acting Assistant Surgeon (Dermatology) in the Office of Dermatoses Investigations of the United States Public Health Service, etc. With a Foreword by FREDERICK K. WEIDMAN, M.D. Pp. 321. New York: Paul B. Hoeber, Inc., 1940. Price, $3.50.

THIS little book fills the gap which exists between bulky texts on dermatology and the quiz compend. The author has acted most sensibly in not pretending to give complete descriptions of dermatoses where such are impossible except in ponderous volumes replete with illustrations and careful descriptions. The merit of this book consists in that the author has indicated the nature of the various dermatoses to a large extent in terms of the pathologist, thus informing the practitioner and the pathologist as to the general setting of such dermatoses in the scheme of medical disease. This is what such specialists desire, rather than to master the intricacies of the dermatologic specialty, such as is required by the formal texts.

To the specialist the book is of value because the recent advances in dermatology have been collected and made available in short form. For the dermatologist who has not had adequate contact with such items the handbook serves as a most useful aid. In this respect it surpasses quiz compends of the conventional type, which are planned rather for the medical student. However, the booklet should be of service to students also, but only in conjunction with their lectures and clinics.

The arrangement of the dermatoses in alphabetical order facilitates ready reference, as in an encyclopedia; this is supplemented by an index remarkably complete and detailed—34 pages in a book of 321 pages.

Therapy is covered with particular respect to physical therapy and other of the more modern modalities. Of course, all of this would be impossible

in a small book had the author not resorted to telegraphic style, and the latter will no doubt appeal strongly to the busy practitioner who needs only a catch word here and there to refresh his memory, or have suggestions offered to him. In short, the author's handbook should fill a definite want for practitioners, dermatologists and students. F. W.

A Text-Book of Occupational Diseases of the Skin. By Louis Schwartz, M.D., Medical Director, U. S. Public Health Service, in charge of Dermatoses Investigations, Washington, D. C.; Lecturer, Department of Dermatology and Syphilology, New York University, etc., and Louis Tulipan, M.D., Clinical Professor of Dermatology and Syphilology, New York University College of Medicine; Consulting Dermatologist, Manhattan General Hospital, etc. Pp. 799; 116 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $10.00.

This work is a valuable contribution to American medical literature and an indispensable manual for those concerned with industrial diseases, including others than those of the skin. It is better systematized, more inclusive of the literature, but not as well indexed as its predecessor, Prosser White's "Dermatergoses." Throughout the work, the authority especially of the senior author, widely known to specialists in this country for his invaluable contributions to this field, is easily recognized. The first-hand descriptions of the manufacturing processes from which occupational dermatoses arise, lends a vividness and realism to the text which carries it beyond the limited confines of merely descriptive dermatology. The work can therefore be a volume of reference for all physicians concerned in industrial medicine, as well as for the dermatologist.

The book comprises 45 chapters, ranging from a brief discussion of workmen's compensation laws in relation to dermatoses, to an analysis of skin hazards in 74 occupations. The chapter on diagnosis is materially, and perhaps not advantageously, shortened by assigning to the dermatologist without differential description such conditions as seborrheic dermatitis, impetigo contagiosa and neurodermatitis, which so frequently defeat the industrial physician and the compensation authority in their encounters with industrial dermatology. Much emphasis is laid on patch-testing and many useful notes on its application with some regard for contributing influences such as perspiration, oiliness, dryness, friction and so forth are provided. Methods of investigation and prevention are briefly discussed and are recapitulated with specific application in many of the ensuing chapters on special industrial irritants. So far as the Reviewer could ascertain, with a limited knowledge of industrial processes but some contact with the problems of industrial dermatology, this work is an encyclopedic catalogue in which at one point or another practically everything that could be conceived as responsible industrially for injury to the skin receives at least brief, and usually illuminating, mention.

What has in the past been a notable deficiency in practical industrial work and in the field of industrial dermatology, is still recognizable, the Reviewer believes, in this book; that is, a lack of adequate discussion and analysis of the host factors so to speak, in the development of occupational dermatitis. The disposition is perhaps natural, to regard the offending substance as overwhelmingly the major part of the picture. A study of the human subject notably from such aspects as constitutional make-up and predisposition, physiologic and pathologic structural and functional abnormality, dietary, climatic and economic and psychologic components has yet to appear. Prosser White, in some of his discussions of industrial dermatology, foreshadowed the need for ultimate comprehension of the collateral influences which play a part and form the background of the irri-

tability of the skin. Industrial dermatology thus studied will be more than a descriptive catalogue of the action of individual irritants and will become an illuminating field for the interpretation of skin and general physiology. The interrelation between allergy and infection, infection-sensitization complexes, interplay between sensitizing contact factors and sweat, sebaceous, vascular and nervous mechanisms of cutaneous disease will go far towards broadening the preventive outlook as well as the actual management of occupational skin diseases.

This suggestion for a greater completeness and a more broadly medical treatment is not offered with any intent to minimize the distinction of the authors' work. J. S.

SKETCHES IN PSYCHOSOMATIC MEDICINE. By SMITH ELY JELLIFFE, M.D., Consulting Neurologist to Manhattan State and Kings Park Hospitals, New York. Pp. 155; 10 figures. New York: Nervous and Mental Disease Monographs, 1939. Price, $3.00.

THE author, one of the first and most distinguished of American psychoanalysts, has long maintained that medical and surgical treatment of physical conditions resulting from prolonged emotional strain, may be attended by dire consequences, unless proper psychologic preparation has been given. From his voluminous writings, the following selection of monographs are offered in support of that contention: What Price Healing?; Psychopathology and Organic Disease; The Death Instinct in Pathology; Dupuytren's Contracture; The Psyche and the Vegetative Nervous System; The Bodily Organs and Psychopathology; The Skin, Nervous System and the Bath; Neuropathology of Bone Disease; Psychoanalysis and Myopia; The Ecological Principle in Medicine. In recent years, much has been written in corroboration of such findings. A bibliography and index are included. N. Y.

THE PROCEEDINGS OF THE CHARAKA CLUB, VOL. IX. Pp. 204; illustrated. New York: RICHARD R. SMITH for The Charaka Club, 1938.

THE ninth volume of the Proceedings of this egregious organization is indeed illustrative of the versatility and virtuosity of its members. Its 30 or more contributions (delivered mostly between 1934 and 1937) range through serious articles on medical history and medical biographic sketches to non-medical essays and poems by physician members. Almost an equal number of unpublished contributions during the same period are listed, some of which, to judge from the titles and from one pungent article here printed, look as if they also would make very entertaining reading.

E. K.

PATHOLOGY. An Introduction to Medicine and Surgery. By J. HENRY DIBLE, M.B. (GLAS.), F.R.C.P. (LOND.), Professor of Pathology in the University of London (The British Post-Graduate Medical School); Late Professor of Pathology at the London School of Medicine for Women, etc., and THOMAS B. DAVIE, B.A. (CAPE), M.D. (L'POOL), M.R.C.P. (LOND.), Professor of Pathology in the University of Liverpool; Late Professor of Pathology in the University of Bristol. Pp. 931; 374 illustrations, including 8 plates in color. Philadelphia: The Blakiston Company, 1939. Price, $10.00.

IN this book the authors have endeavored "to present pathologic changes to the student in a series of *processes* going on in the living body and leading to certain consequences—signs, symptoms, functional changes and morbid anatomical results." Possibly because of these aims, admirable though they are, the several parts of the book are of unequal merit. There is an

overlong discussion of subject matter usually included in textbooks on bacteriology and immunology; and in consequence, many subjects usually discussed in parts devoted to special pathology receive scant notice. On the other hand, a number of chapters in the field of general pathology (*e. g.*, fatty changes) are fully and well treated.

There are no references to original sources, though names of prominent investigators are used. This omission, in the Reviewer's opinion, is a mistake; medicine is a graduate study and the student should be directed to the literature lest he develop a mistaken sense of dependence on the authority of the textbook.

Taking the work as a whole, it does not appear to be as suitable for courses in pathology in American universities as several texts now available.

B. L.

DIAGNOSTIC SIGNS, REFLEXES AND SYNDROMES (STANDARDIZED). By WILLIAM EGBERT ROBERTSON, M.D., F.A.C.P., Visiting Physician, Medical Division, Philadelphia General, St. Luke's and Children's and Northeastern Hospitals, and HAROLD F. ROBERTSON, B.S., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Assistant Visiting Physician, Medical Division, Philadelphia General and Methodist Hospitals. Pp. 309. Philadelphia: F. A. Davis Company, 1939 Price, $3.50.

NOT just a routine collection of signs, largely eponymic (although a malevolent State-Board medical examiner might find here much devastating material), but a careful compilation of diagnostic aids, well tinctured by the clinical experience of the compilers. In alphabetical order are given not only the signs, but diseases in which they occur and organs to which they are referred. The work should be helpful for reference by physicians and students.

R. K.

LEHRBUCH DER AUGENHEILKUNDE. By DR. ERNST FUCHS, Sechzehnte, vermehrte und verbesserte Auflage neu bearbeitet, VON DR. ADALBERT FUCHS, a. o. Professor der Augenheilkunde an der Universität in Wien. Pp. 904; 362 text illustrations and 5 colored plates. Wien: Franz Deuticke, 1939. Price, Paper, M. 27; Bound, M. 30.

FOR many years Fuchs' text book translated by Duane was the standard American text. When Dr. Duane died this book rapidly went out of print and copies are being sold at a premium. Although this present text is in German, it retains all the best features of the English translation and brings the subject matter up to date. It will be a valuable addition to the libraries of all ophthalmologists who read German fluently.

F. A.

CÆSAREAN SECTION. Lower Segment Operation. By C. MCINTOSH MARSHALL, F.R.C.S. (ENG.), Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. Pp. 230; 107 illustrations and 2 colored plates. Baltimore: The Williams & Wilkins Company, 1939. Price, $6.50.

THIS volume deals with the operative aspect of the intraperitoneal lower segment Cæsarean section operation. It includes an extensive review of the literature and the author's experience, based upon the performance of 250 operations. The history of the operation is well treated in the introductory chapter. The remaining chapters deal with anatomy, incisions, anesthesia, the technique of the lower segment operation, infection, hemorrhage, the use of oxytocics, the place of the operation in cases of placenta prævia, the difficulties and dangers of the operation and the authors results.

The book is well arranged and profusely illustrated. There are numerous

paragraph headings which make it a good reference volume. The bibliography is very extensive, but the lack of titles detracts greatly from its value for the research investigator, in the opinion of the Reviewer. For the practicing operating obstetrician the volume should be an extremely one.

D. M.

FUNDUS ATLAS. Stereoscopic Photographs of the Fundus Oculi. By LOUIS BOTHMAN, B.S., M.D., F.A.C.S., Clinical Professor of Ophthalmology, The University of Chicago; Associate Ophthalmologist, St. Luke's Hospital, Chicago, and REUEL W. BENNETT, Photographer for the Division of Ophthalmology, The University of Chicago Clinics. Pp. 50; 50 original stereoscopic photographs. Chicago: The Year Book Publishers, Inc., 1939. Price, $17.00.

THIS collection of fifty plates for use in a stereoscope will be found useful for teaching ophthalmoscopic diagnosis. The plates were made from fundus photographs taken with the Nordensen camera and magnified three or more times the size of the original negatives. On each card is a history of the case and a description of the various details which are to be found.

F. A.

THE RISE OF EMBRYOLOGY. By ARTHUR WILLIAM MEYER, Professor of Anatomy, Emeritus, Stanford University. Pp. 367; 95 illustrations. Stanford University: Stanford University Press, 1939. Price, $6.00.

THE author has elected to treat his subject by tracing separately the history of the great problems of embryology, *e. g.*, spontaneous generation, the ovum, the spermatozoön, and so on. This method has obvious advantages, but it scatters the work of a single investigator, perhaps failing to give a picture of the man and his accomplishments. Of special interest to the physician is a chapter on the development of visual and technical aids and another dealing with malformations. Quotations are freely used throughout the book, which is well illustrated and closes with an excellent 19-page bibliography. The index, however, is regrettably brief.

H. S.

ATLAS OF SURGICAL OPERATIONS. By ELLIOTT C. CUTLER, Moseley Professor of Surgery, Harvard University and Chief Surgeon of the Peter Bent Brigham Hospital; Formerly Professor of Surgery, Western Reserve University, and Director of Surgery of the Lakeside Hospital, and ROBERT ZOLLINGER, Associate Professor of Surgery, Harvard University, and Senior Associate in Surgery at the Peter Bent Brigham Hospital. Pp. 181; 84 plates. New York: The Macmillan Company, 1939. Price, $8.00.

THIS is a unique atlas. There is a chapter on surgical technique, one on anesthesia and one on pre- and postoperative care. The remainder of the volume consists of 84 large plates showing the technique of a variety of operations, with a page opposite each plate in which there is briefly discussed the indications for operation, the preoperative preparation, the anesthesia, the position of the patient, the operative preparation, the incision and exposure, the details of operation and the postoperative care. The illustrations are done in black and white line drawing. They are exceedingly simple yet nevertheless very well done.

This volume will prove very useful to all surgeons, whether young or old. Within a page or two one can obtain knowledge of certain standardized surgical procedures. The many illustrations on a single plate make it possible to visualize the steps of the operation from beginning to end on a single page.

Drs. Cutler and Zollinger are to be congratulated on the splendid piece of work they have done, but the Reviewer must also congratulate the artist who has so acceptably depicted the operative procedures. Every surgeon would not do every operation in the same way, but this is a volume that every young surgeon can use and follow with benefit to himself and to the patient. Many of the more competent technicians in surgery could well heed the constant admonition on the gentle handling of tissues, the necessity of completing the hemostasis, and the necessity of adequate exposure.

I. R.

A Topographic Atlas for X-ray Therapy. By Ira I. Kaplan, B.S., M.D., Director, Radiation Therapy Department, Bellevue Hospital; Director, Division of Cancer, Department of Hospitals, City of New York, etc., and Sidney Rubenfeld, B.S., M.D., Associate Visiting Radiation Therapist, Bellevue Hospital; Instructor in Surgery, New York University Medical College, etc. Pp. 120; 55 full page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, $4.00.

This atlas is admirably suited for teaching purposes. It contains 55 excellent diagrammatic illustrations dealing with different diseases. Each clearly presents the normal visible anatomic landmarks and the palpable internal landmarks. The diseased organs are outlined within the body. The relative size, number, and position of each treatment cone used is clearly indicated. Printed in outline form opposite each illustration is a verbal description of each illustration. The fundamental mechanics of applying Roentgen therapy are all referred to, except physical factors of dosage. The authors have deliberately avoided consideration of the latter, so that the reader will not find any mention of the amount and quality of radiation to be used in various conditions.

P. H.

Argyria. The Pharmacology of Silver. By William R. Hill, M.D., Instructor in Dermatology and Syphilology, University of Pennsylvania, and Donald M. Pillsbury, M.A., M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania. Pp. 172. Baltimore: The Williams & Wilkins Company, 1939. Price, $2.50.

This little monograph covers more than the subject indicated in the title: there are chapters on the history of argyria, its absorption and excretion, its deposition in tissues, the pharmaco-physiologic effects, the diagnosis and treatment, an analysis of reported cases, and its hygiene. Argyria of the eye and industrial argyria also occupy chapters. The bibliography numbers 601 references and there are complete author and subject indexes. Most useful, too, is a list of proprietary silver compounds; it is surprising that they should number a hundred or more.

The subject is treated from the biologic viewpoint throughout, with attention to detail, dispassionately and judicially. The authors have rendered a distinct service in bringing the subject down to date in such a complete, authoritative and scientific manner.

F. W.

NEW BOOKS.

On Oxidation, Fermentation, Vitamins, Health and Disease. (The Abraham Flexner Lectures, Series No. 6.) By Albert V. Szent-Györgyi, M.D., Ph.D. (Cantab.) D. H. C., Prix Nobel, Professor of Medicine and Organic Chemistry. University of Szeged. Pp. 109. Baltimore: The Williams & Wilkins Company for Vanderbilt University, 1939. Price, $2.00.

New Facts on Mental Disorders. Study of 89,190 Cases. By NEIL A. DAYTON, M.D., M.C., Director, Division of Statistics and Director, Division of Mental Deficiency, Massachusetts State Department of Mental Health, etc. Pp. 486; 110 graphs; 84 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, $4.50.

Pneumoconiosis (Silicosis). The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 56 and Appendix (47 pages); illustrated. New York: John B. Pierce Foundation, 1940. Price, $1.00.

Sex and Life: Forty Years of Biological and Medical Experiments. By EUGEN STEINACH, M.D., PH.D., Formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by JOSEF LOEBEL, M.D. Pp. 252; 67 illustrations (many in color). New York: The Viking Press, 1940. Price, $3.75.

The Medical Clinics of North America, Vol. 24, No. 1 (Chicago Number—January, 1940). Pp. 283; 37 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This Chicago number presents a timely symposium of 14 articles (comprising about two-thirds of the volume) on various practical aspects of geriatrics. As a useful complement to the less clinical aspects of the subject comprised in the recent volume on Problems of Ageing (Baltimore, The Williams & Wilkins Company, 1939), this part of the volume might well have been even further amplified.

The Specific Therapy of the Pneumonias. By JESSE G. M. BULLOWA, M.D., Clinical Professor of Medicine, New York University College of Medicine. (Beaumont Lecturer for 1939.) Pp. 80; illustrated. (Reprinted from the Journal of the Michigan State Medical Society, July-August, 1939.)

Clinical Toxicology. By CLINTON H. THIENES, M.D., PH.D., Professor of Pharmacology and Head of the Department of Pharmacology, School of Medicine, University of Southern California, Los Angeles; Attending Pathologist (Toxicology), Los Angeles County Hospital. Pp. 309; 7 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $3.50.

Orthopedic Operations. Indications, Technique and End Results. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City. Pp. 766; 865 illustrations on 322 figures. Springfield, Ill.: Charles C Thomas, 1940. Price, $9.00.

Le Débit Cardiaque. Etudes Expérimentales et Cliniques. By JEAN LEQUIME, Agrégé de l'Enseignement supérieur Assistant a l'Université de Bruxelles. Preface by Professeur Paul Govaerts. Pp. 223; illustrated. Paris: Masson et Cie, Editeurs, 1940. Price, 40 francs.

Das Antlitz der Blindheit in der Antike. Eine medizinisch-kulturhistorische Studie. By A. ALBERT M. ESSER, Dr. med et phil. Pp. 178. Stuttgart: Ferdinand Enke, 1939. Price, Paper, Rm. 9.50; Bound, Rm. 11.00.

Carbohydrate Metabolism. Four pages presented in a Symposium held at the meeting of the American Physiological Society at Toronto, Canada, April 29, 1939. Chairman: PROFESSOR C. H. BEST. (Reprinted from Endocrinology, Vol. 26, No. 2, February, 1940.) Pp. 66; illustrated. Menasha, Wis.: The George Banta Company, 1940. Price, $1.00.

This consists of reprints of four interesting papers presented in a Symposium of the American Physiological Society. They deal with a résumé of each author's experimental work, in relation to the work of others, on the rôle of enzymes, the liver, the adrenal cortex, and the pituitary in carbohydrate metabolism. I. Z.

Directory of Medical Specialists. Certified by American Boards. PAUL TITUS, M.D., Directing Editor. Pp. 1573. New York: Columbia University Press, 1940, for The Advisory Board for Medical Specialties. Price, $3.50.

Injuries of the Skull, Brain and Spinal Cord. Neuro-Psychiatric, Surgical, and Medical-Legal Aspects. Edited by SAMUEL BROCK, New York University. Contributors: B. J. ALPERS, ABRAM BLAU, K. M. BOWMAN, SAMUEL BROCK, JEFFERSON BROWDER, BRONSON CROTHERS, L. M. DAVIDOFF, T. K. DAVIS, CHARLES DAVISON, C. G. DYKE, C. A. ELSBERG, A. R. ELVIDGE, E. D. FRIEDMAN, F. C. GRANT, C. C. HARE, G. B. HASSIN, MOSES KESCHNER, M. M. PEET, W. R. RUSSELL, PAUL SCHILDER, C. P. SYMONDS. Pp. 632; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, $7.00.

Non-Profit Hospital Service Plans. Historical and Critical Analysis of Group Hospitalization, a non-profit, non-political application of the principle of insurance to the purchase of hospital care. By C. RUFUS ROREM, PH.D., C.P.A., Director, Commission on Hospital Association, Chicago. Pp. 130. Chicago: Commission on Hospital Service, 1940. Price, 50¢.

The Medical Career and Other Papers. By HARVEY CUSHING. Pp. 302. Boston: Little, Brown & Co., 1940. Price, $2.50.

Preclinical Medicine. Preclinical States and Prevention of Disease. By MALFORD W. THEWLIS, Attending Specialist, General Medicine, United States Public Health Hospitals, New York City; Special Consultant, Rhode Island Department of Public Health, etc. Pp. 223; 12 figures. Baltimore: The Williams & Wilkins Company, 1939. Price, $3.00.

Heil Hunger! Health Under Hitler. By DR. MARTIN GUMPERT, Translated from the German by MAURICE SAMUEL. Pp. 128. New York: Alliance Book Corporation, 1940. Price, $1.75.

Syphilis and Its Accomplices in Mischief: Society, the State and the Physician. By GEORGE M. KATSAINOS, M.D. Pp. 554; Athens, Greece: Privately Printed, 1939. Price, $4.75. (Author's address, 132 Hemenway St., Boston, Mass.)

Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases. By EGON BRUUN. Pp. 229; 49 illustrations. Copenhagen: Einar Munksgaard. Price, Dan. Kr. 24.00.

Shock, Blood Studies as a Guide to Therapy. By JOHN SCUDDER, M.D., MED. SC.D., F.A.C.S. From the Surgical Pathology Laboratory of the College of Physicians and Surgeons, Columbia University, and the Department of Surgery, the Presbyterian Hospital, New York City. Pp. 315; 58 illustrations, and 5 plates (3 in color). Philadelphia: J. B. Lippincott Company, 1940. Price, $5.50.

Modern Diabetic Care. Including Instructions in the Diet and the Use of the Old and New Insulins. By HERBERT POLLACK, A.B., PH.D., M.D., Instructor in Clinical Medicine, Cornell Medical College; Chief of the Diabetic Clinic, Mt. Sinai Hospital, New York City, etc. Pp. 216. New York: Harcourt, Brace & Co., 1940. Price, $2.00.

NEW EDITIONS.

A Textbook of Surgery. By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from Lectures and Other Writings of 23 Members of the Surgical Department of The Harvard Medical School. Pp. 1272; 530 illustrations by Willard C. Shepard. Fourth Edition. Springfield, Ill.: Charles C Thomas, 1940. Price, $8.00.

The Management of Obstetric Difficulties. By PAUL TITUS, M.D., Obstetrician and Gynecologist to The St. Margaret Memorial Hospital, Pittsburgh; Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, and to The Homestead Hospital, Homestead, Pa. Pp. 968; 368 illustrations and 5 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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ENDOMETRIOSIS.

ALTHOUGH it is less than 20 years since Sampson[13] presented his outstanding work on perforating hemorrhagic cysts of the ovary, the interest aroused in this fascinating subject continues unabated. Of the various names suggested for this condition the term "endometriosis" has been generally accepted, signifying a disease in which non-malignant but often invasive growths are found which are composed of gland-like structures resembling endometrial glands. An important characteristic of these lesions is that, like endometrium, they react to hormonal stimulation from the ovary, enlarging during the congestive premenstrual phase of the menstrual cycle and decreasing in size during the resting phase. While at first these growths were found only in the pelvic cavity, principally in the ovary, further investigation has shown that they may involve various structures both within and outside the pelvis. From the clinical aspect the subject has been well reviewed by Counseller[5] of the Mayo Clinic, with a discussion of the various hypotheses concerning the pathogenesis of this condition. He has grouped these hypotheses into three classes: 1, embryonic; 2, metaplastic; and 3, migratory. The embryonic hypothesis would include the Wolffian theory of von Recklinghausen and the Muellerian hypothesis favored by Cullen, in each of which the growths are supposed to arise from embryonic structures. These theories can only explain the endometriomas in the immediate vicinity of the uterus where these embryonic rests could exist and Counseller believes that these theories at the present time are of historical interest only. Concerning the metaplastic hypotheses, he recalls that Iwanoff first suggested a serosa-epithelial metaplasia of the peritoneum, which at present is usually known as the theory of Meyer who advanced it further. According to this theory, under the influence of an inflammation or of an ovarian hormonal action, the pelvic peritoneum might form tubular invaginations which would sink more or less deeply into the tissues of subjacent organs. At the same time, the flat endothelium of the involved peritoneum might become transformed into columnar epithelium, thus producing an adenomatous appearance. Although

the common celomic origin of the peritoneum, the ovary and the Muellerian ducts might be consistent with this hypothesis, it seems that they assume profound histologic and physiologic changes for adult peritoneum. While it is clearly established that the ovarian hormones have an important effect on fully developed endometriomas, it is not established that they might initiate the development of these lesions.

The final or migratory hypothesis assumes that the endometrial tissue in endometriosis has its origin in the uterine mucosa, although it may become transplanted in several ways. It is generally accepted, as suggested by Cullen, that adenomyomas of the uterus illustrate an invasion of the uterine musculature by its endometrial lining, or invasion by contiguity. Sampson's hypothesis of retrograde menstruation with possible incubation of endometrial implants in the ovary is perhaps the most generally accepted theory. In operations performed during the menses, blood has frequently been seen coming from the tubes. However, the grafting in the pelvis of devitalized endometrial elements found in menstrual blood is speculative and this hypothesis does not explain endometriosis of the groin or of the umbilicus. Another subdivision of the migratory hypothesis is that of lymphatic metastasis. According to this theory it is assumed that during menstruation, by virtue of the indefinite limit between endometrial tissue and the subjacent tissues, epithelial elements may enter open lymphatic vessels and be carried to the subserosal lymphatics or to the uterosacral ligaments, the broad ligaments, the ovaries, the round ligaments or the abdominal wall. The known lymphatic drainage of the uterus enables the tracing of a possible course to all of the locations in which endometriosis has been seen, including laparotomy scars. Counseller believes that this theory explains the histopathologic phenomena in endometriosis more adequately than any other.

Endometriosis is an extremely important disease of young women and its most predominant symptom is dysmenorrhea of an acquired or progressive type. Vesical and rectal pain superimposed upon dysmenorrhea is almost always diagnostic, while diffuse pelvic soreness, brought about by walking or jarring of the pelvis in any way, is also suggestive. He believes that in the majority of cases radical surgical treatment should be employed, in fact radical treatment was carried out in about 80% of a series of 884 cases at the Mayo Clinic. Cases in which conservative procedures are to be carried out must be very carefully selected if recurring lesions and subsequent treatment are to be avoided. The percentage of recurrences will be reduced by limiting conservative treatment to those in which relatively few surgical procedures will be required to remove the disease. He believes that it is safer to err on the side of radicalism than to attempt preservation of ovarian function in those cases in which there is some involvement of both adnexa or in which there is considerable involvement of one side and the adjacent uterine wall. At the Clinic they feel that the upper age limit for conservative procedures is between 37 and 40 years but the extent of the lesions and their location are more important in selecting the type of operation than is the age of the patient. It has been their observation that when it is necessary to perform radical hysterectomy for endometriosis before the menopause, the patients do not experience the severe menopausal symptoms that those patients do who undergo a similar

operation for conditions other than endometriosis. They have not been able to show that conservative procedures are of much value in the elimination of sterility since only 7 of the 55 patients whom one could reasonably expect to become pregnant did become so; in fact, pregnancy can only be expected in those cases in which the disease is limited to one side or to a relatively few implants which can be excised. While it is possible to castrate these patients by irradiation rather than by operation, it is his belief that patients under the age of 40 should be submitted to surgical treatment because it is impossible to determine clinically whether complete cessation of ovarian function is advisable. Furthermore, it is much wiser to know whether there is any other associated pathologic condition of the pelvic organs before submitting the patient to castration by radium or Roentgen rays. The one exception to this rule may be a large adenomyoma of the rectovaginal septum which cannot be removed surgically without considerable risk of producing a rectal fistula.

In analyzing his series of 112 cases, Allen[1] was impressed by several features of the disease, namely, the high incidence of menstrual irregularities, the regular appearance of associated benign uterine tumors, the marked prevalence of relative sterility and the wide distribution of the lesions. The marked irregularities in the menstrual habit suggests to him a glandular imbalance and would explain those instances of irregular bleeding occurring in patients in whom the lesions were insignificant or so located that they could not very well have been the mechanical cause of change in the menstrual flow. Bleeding occurred from the endometrium in all stages of development, although that representing the Swiss cheese type of hyperplasia was the most common. The high incidence of fibromyomas in this series was noteworthy and on first thought might explain the increase in bleeding and high incidence of sterility but it seems more logical to him to include these masses of functionless tissue as an end-result of hormonal cell stimulation due to an underlying glandular dysfunction. The wide distribution of the lesions necessitates the acceptance of either the Sampson theory or the theory of metaplasia, the latter pointing to some increased hormonal activity. The high incidence of sterility, in spite of patent tubes and potent mates, suggests some disturbance in physiology rather than mechanical interference since sterility is a common result of glandular imbalance characterized by menstrual irregularities. On the whole, therefore, he feels that endometriosis is a manifestation of cellular metaplasia caused by glandular dysfunction and until we know more about their action prolonged administration of potent glandular products may be fraught with danger.

Of 375 cases of endometriosis reported by Pemberton,[10] 66% had radical operations and 34% were treated by conservative methods, either operative or irradiation. There was only one death in the whole series. Of the cases treated by conservative measures, 29% needed further treatment. He believes that Roentgen ray should be used for secondary treatment if the chief symptom is menorrhagia or dysmenorrhea but not under other circumstances. He is cautious in the use of radium in these secondary cases because the intestine may be adherent to the uterus and therefore may be devitalized by radium placed within the uterus. Pregnancy occurred after conservative operation in 19 of

the 76 patients in whom it might have been expected, so that for this reason alone be believes that a conservative operation will often be indicated. If pregnancy is not a factor in the decision as to the type of operation he feels that it is better to perform a hysterectomy with bilateral oöphorectomy because of the high percentage of failure of the conservative operations.

In contrast to the radical views concerning treatment which have thus far been presented is the report from the Lahey Clinic of a small series (43 cases) reported by Cattell and Swinton.[4] They have found that a preoperative diagnosis of endometriosis is seldom made; 3 such cases were recognized before operation in their series and several more had this tentative diagnosis, one was an obvious lesion of the round ligament while the other two caused obstruction of the sigmoid at the time of menstruation. Ovarian endometriosis will always be difficult to differentiate from chronic pelvic inflammation but such symptoms as abnormal menstruation, sterility, acquired dysmenorrhea and lower abdominal pain should make one consider endometriosis particularly when associated with a fibroid uterus or malpositions of the uterus which interfere with its drainage. They agree with the preceding authors that the treatment of this condition depends on the extent and location of the lesion, the age and the general physical condition of the patient, but complete involvement of the ovaries and the necessity for castration have been rare in their experience. Three of their patients have had children following the removal of one ovary for endometriosis. They feel that the removal of all ovarian tissue in young women is a very serious matter and is not warranted in this disease where local excision can be performed. In women over 40 years of age supravaginal hysterectomy with removal of the tubes and ovaries is indicated. In poor risk patients, it is to be remembered that castration will cause the lesion to recede and usually relieve symptoms. In this group the production of an artificial menopause through the use of Roentgen ray therapy should be considered. In the rectovaginal group where intestinal obstruction has not occurred, the disease can be relieved by local excision followed by the production of an artificial menopause. Where intestinal obstruction has occurred, the obstruction must first be relieved by colostomy. This colostomy should be done in such a manner that it can later be closed, since following the removal of the ovaries the lesion will regress and the obstruction will be relieved. In bladder endometriosis, the production of an artificial menopause will cause the lesion to disappear. In endometrial tissue in the appendix, the removal of that organ will end all trouble while local excision will usually cure other types of endometriosis. In a word, they have found that the end results after both conservative and radical operations are satisfactory in properly selected cases.

Endometriosis of the Bladder. In a review of reported cases of bladder endometriosis, including one of his own, Henriksen[6] has found that a fairly constant symptom complex presents itself, although a few have been asymptomatic from a urinary standpoint. In the majority of the cases frequency, dysuria and hematuria appear several days before menstruation, persist during the flow and continue for a day or even a week after its cessation. The course of the disease is chronic, starting first with a slight discomfort, which is constant but not aggra-

vated by the menstrual periods, though later the clinical picture changes, the following description being fairly typical. Increased frequency of urination both by day and by night is the most common complaint and as a rule completely disappears between the periods. Dysuria varies but usually occurs at the end of micturition, more as a sense of discomfort than as actual pain. Hematuria, because of its microscopic nature, is rarely noted by the patient and is present only during menstruation or just preceding it. There is a marked variation in the severity of the symptoms depending on the size and topographic location of the tumor within the bladder, as well as the degree of tissue reaction during the menstrual period. When the ureters are encroached on there is the added symptom suggesting kidney involvement. The youngest patient in the group was 19 years of age. There is apparently, however, a predilection for the decade between 35 and 45 years and except for one case, all have occurred during menstrual life. As a rule the tumors are located within the floor of the bladder, just above or between the ureters, peculiarly more toward the right side. They are rarely found in the vertex and though they may involve the trigone, the involvement is through extension. The size of the tumors is fairly constant, being generally between 2 and 4 cm. and they usually present a distinctly nodular surface. The treatment of this tumor cannot be prescribed dogmatically. The size, location, age and general condition of the patient are the deciding factors as to which of the two possible therapeutic procedures is best suited. Complete excision is the method of choice in young women desirous of children and in whom the margin of bladder tissue safety is sufficient, while castration is done, either by operation or by irradiation, in patients near the menopause or in whom the growth is too extensive for excision, or when the general condition of the patient contraindicates surgical measures. Since there are cases presenting an atypical picture, this tumor may easily be mistaken for a malignant lesion of the urinary bladder.

In presenting a complete history of a case of this disease, beautifully illustrated with colored plates, Phillips[11] reviews 29 cases previously reported in the literature. He believes that the incidence of bladder endometriosis is far greater than reported and would be found if the cystoscope were used more frequently in diagnosis. The possibility of the disease should always be thought of in a patient suffering from frequency of urination, dysuria and hematuria. When this triad is cyclical and is exacerbated during the period and one finds on cystoscopic examination that "blue-black" cysts and "endometriotic edema" are present, the diagnosis of endometriosis of the bladder is certain. He believes that the method of choice in treatment is by the induction of an artificial menopause with Roentgen ray. Surgical interference, however, is indicated in those few cases in which the patient is considerably under the menopause age and is desirous of children. In reporting a single case of his own, Reynolds[12] corroborates practically everything that Phillips has stated and agrees with him as to the choice of treatment.

Endometriosis of the Umbilicus. Presenting 2 cases of his own and collecting over 70 cases from the literature, Weller[15] states that the umbilicus cannot be regarded as a rare location for endometriosis. In this location smooth muscle is not often present so that the term "adenomyoma" is inappropriate. The sweat glands, which have been men-

tioned repeatedly in connection with umbilical endometriosis, have no part in the genesis of this condition. The origin of the disease in this location is explainable only with the greatest difficulty under the implantation and metastasis theories but is readily understandable under the various modifications of the serosal theory. For those especially interested in umbilical endometriosis, the article of Boggs[2] is heartily recommended since in addition to reporting his own case very well, 96 other cases from the literature are reported chronologically and a complete bibliography of the subject is appended. He reminds us that this condition always occurs during the years of ovarian activity and the cyclic nature of the symptoms, corresponding to the menstrual periods, will usually suggest endometriosis. The symptoms include the secretion of a blood-tinged fluid from the navel and pain, tenderness, swelling, itching and bluish discoloration. The tumors usually reach full size in from 2 to 6 months, ranging from 1 to 3 cm. in diameter, occasionally reaching a diameter of 5 cm. These tumors must be differentiated from uterine fistulas, which also may produce menstruation. The treatment of choice is wide excision, the technique being that used for hernial repair. It is interesting to note that in the case he reports, the patient was an unmarried woman of 49 years who had had a hysterectomy 2 years previously. This was followed by a period of amenorrhea until menstruation from the umbilicus began, but she never had further vaginal bleeding.

Rare Forms of Endometriosis. A case of *endometrioma of the perineum* has been recorded by Maliphant[8] who presents 3 other cases collected from the literature. The case recorded occurred in a patient operated upon for a lacerated perineum. The day after operation she menstruated and 2 years later a tumor developed in the perineal scar which showed the typical structure of uterine mucosa. The history is very suggestive that this tumor was a true implant and that it had grown from a fragment of exfoliated uterine mucosa in the menstrual discharge.

At the Lahey Clinic according to Cattell,[3] 16.3% of the 104 patients with endometriosis had intestinal symptoms due to *involvement of the sigmoid and rectum*. The diagnosis is seldom made preoperatively but should be suspected when the obstruction is long standing and is worse at the time of menstruation, when there are associated pelvic findings and when the local lesion on examination by the sigmoidoscope and barium enema is not typical of carcinoma. The condition can usually be readily recognized at operation. Because of the complicating intestinal involvement, the operative treatment must be directed not only to the ovaries but to the intestinal lesions as well. It is sometimes necessary to resect the sigmoid but often removal of the ovaries is all that will be necessary since the growth will regress after the artificial menopause with its accompanying loss of ovarian hormone. In cases of severe intestinal obstruction due to this lesion, a temporary colostomy will have to be made.

Schumann and Parke[14] report 2 cases in which endometriosis occurred in *laparotomy scars* and they comment that almost all of the reported cases follow a Cesarean section or pelvic laparotomy although several have followed an appendectomy. These endometriomas usually present themselves as fairly firm, nodular masses rarely larger than 3 or 4 cm.

in diameter, lying in the laparotomy scar and sometimes enlarge and even discharge blood at the menstrual period. They may or may not produce localized pain, are usually attached to the sheath of the rectus muscle and rarely penetrate the parietal peritoneum. They have found no report of a malignancy developing in an abdominal endometrioma. After a discussion of the theories of origin of these tumors, such as has been presented previously in this review, they conclude that the mechanical implantation theory of Sampson is the only logical explanation for the appearance of these implants in abdominal scars.

Three cases are reported by Neel[9] from the Mayo Clinic in which endometrial tumors were present in the *inguinal region*. In the first case, the menses were regular and without pain and there had been no previous operation. In the second case, a right herniorrhaphy had been performed 18 years previously and the incision had drained for 4 months. Pain and soreness in the inguinal region were more pronounced during menstruation. In the third case, an appendectomy had been done 17 years previously and for 2 years preceding admission the patient complained of pain over the lower right abdominal quadrant at each menstrual period, often persisting for 10 or 15 days after the period. Although these tumors, often called adenomyomas, may occur at any point in the round ligament from its uterine attachment to its termination in the labium majus, they are said to be 3 times as common in the extraperitoneal portion of the ligament as in the intraperitoneal portion and are usually found near the external inguinal ring. The frequency with which an inguinal hernia is associated is very striking. The diagnosis of a typical lesion should offer no difficulty. The presence of a more or less fixed, irreducible swelling in a woman in the childbearing age, which is more prominent and more painful during each menstrual period, or is associated with discomfort which is more pronounced following the menstrual period, should lead one to suspect the true nature of the tumor. In one of the cases reported in the literature the patient complained of an abscess of the vulva which had been discharging for 2 years and which had caused throbbing pain during menstruation. In another case, the inguinal mass had been mistaken for a broken down lymph node and had been incised after which a sinus developed and blood had been discharged at each menstrual period. If the tumor is asymptomatic, the diagnosis will probably be made only by the pathologist.

The experimental production of *endometrial transplants in the lungs* of rabbits has been demonstrated by Hobbs and Bortnick.[7] These experiments have also demonstrated that endometrial tissue can be transported through the veins to the lungs. (They[7] have recorded the history of a woman of 42 which, while lacking positive proof, strongly suggests the diagnosis of endometriosis of the lung.—C. C. N.) Endometrial tissue has been demonstrated in the lumina of veins and lymphatics by other investigators and an abundance of information has been recorded from which one can deduce that uterine mucosal tissue must be transported through the lymph and blood vascular systems. With the fact established that such tissue is transported through these systems and that the tissue will grow in the lungs, they believe that it is logical to assume that uterine mucosa does occasionally become implanted in the lungs. It is also plausible that this tissue might rarely be found

in any organ in the body, since it may get into the left heart either by passing through a patent foramen ovale or by propagating through the capillaries of the lungs into the pulmonary veins and thence into the left heart. With this possibility of wide dissemination in mind, a credible theory for the explanation of vicarious menstruation becomes evident since it may be due to endometrial transplants in the area from which the periodic bloody discharge issues.

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REFERENCES.

(1.) **Allen, E.**: Am. J. Obst. and Gynec., **26**, 803, 1933. (2.) **Boggs, R.**: Arch. Surg., **37**, 642, 1938. (3.) **Cattell, R. B.**: New England J. Med., **217**, 9, 1937. (4.) **Cattell, R. B.**, and **Swinton, N. W.**: Ibid., **214**, 341, 1936. (5.) **Counseller, V. S.**: (*a*) Am. J. Obst. and Gynec., **36**, 877, 1938; (*b*) Ibid., **37**, 788, 1939. (6.) **Henriksen, E.**: J. Am. Med. Assn., **104**, 1401, 1935. (7.) **Hobbs, J. E.**, and **Bortnick, A. R.**: Surg., Gynec. and Obst., **69**, 577, 1939. (8.) **Maliphant, R. G.**: J. Obst. and Gynec., Brit. Emp., **40**, 957, 1933. (9.) **Neel, H. B.**: Proc. Staff Meet. Mayo Clin., **12**, 766, 1937. (10.) **Pemberton, F.**: New England J. Med., **217**, 1, 1937. (11.) **Phillips, R. B.**: J. Obst. and Gynec., Brit. Emp., **41**, 165, 1934. (12.) **Reynolds, L. R.**: J. Urol., **41**, 157, 1939. (13.) **Sampson, J. A.**: Arch. Surg., **3**, 245, 1921. (14.) **Schumann, E. A.**, and **Parke, W. E.**: Am. J. Obst. and Gynec., **28**, 222, 1934. (15.) **Weller, C. V.**: Am. J. Path., **11**, 281, 1935.

DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF

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THE COSTS OF SYPHILIS.

To gain insight into the monetary needs for the effective control of syphilis, it is highly desirable to collate what information is available in the recent literature on the cost of syphilis. We must recognize that any attempt to determine and correlate these costs at present results only in a gross approximation. Such a compilation is of limited usefulness also, as the costs, both direct and indirect, vary from time to time and from locality to locality. Not only are the figures few and inaccurate, but the costs themselves are of an indefinable character. In the direct costs of medical care the proportion of the expenditure necessitated by the incidental finding of syphilis among the recipients of service is a fraction which defies calculation. The indirect costs are even more vague, and their extent is a matter of conjecture. In this attempt to assemble the most important of the available con-

tributions to this subject, we recognize the shortcomings of the data, as well as the deficiencies in the methods by which they were obtained.

Certain individuals in this country have been especially prominent in the effort to arrive at an idea of the costs of syphilis to the individual and to the community as a whole. Among them are Keidel[18] of Baltimore, Loeffler[20] of St. Louis, Bromberg and Davis[5,9] of Chicago, Brumfield[6,40] of Albany, N. Y., and his associates of Baltimore, Goldberg[14a,b] of New York, Rice[34] of the United States Public Health Service, and Nelson[29a,b,c] of Massachusetts. In keeping with the lack of definition of the costs of syphilis, some of these individuals criticize each other's methods of approach, but derive figures with a surprisingly similar trend.

The magnitude of the costs of syphilis can be surmised from the incidence and prevalence figures for this disease in the United States, as given by Vonderlehr, Usilton, and Nelson.[29b,44,45,46] On the basis of one-day cross-sections and other statistical determinations, it is now definitely known that the minimum number of persons in the United States constantly in need of medical care because of syphilis is near 683,000, or 4 per 1000 population. Furthermore, in the United States annually 500,000 cases of early syphilis seek authorized medical care. In addition, there is a large undetermined number of individuals acquiring the infection who neglect treatment until some late manifestation forces them to have attention.

Vonderlehr and Usilton (1938)[46] showed that "the probability of acquiring syphilis sometime in life is 1 out of 10." This statement is founded on the annual attack rate applied to 100,000 individuals born alive and followed throughout life. Although the annual attack rate seems low, when cumulated so as to indicate the probability of acquiring syphilis by a given age, it is found that one-tenth of the people before the attainment of the 50th year of life will have acquired syphilis, out of every 100,000 born alive. This rate is usually lower than that found on routine serologic examination of persons tested under the antenuptial physical examination laws, in industry or any random sample of the population. Vonderlehr and Usilton[46] give several reasons for these differences: *a*, Many persons in a random sample are still in danger of acquiring the infection, but have not yet acquired it; *b*, the blood test for syphilis becomes negative, either spontaneously or as the result of treatment in many infected persons; *c*, death removes from the population a high proportion of those who are infected.

Vonderlehr and Usilton also show that treatment decreases the probability of a disastrous outcome in syphilis, so that serious late manifestations, such as neurosyphilis and cardiovascular syphilis are greatly diminished.

The Cost of Treatment of a Syphilis Patient. In 1919 Stokes[38] estimated that for patients of moderate means, the fee cost or cost to the patient of treatment of secondary syphilis in private practice was seldom less than $500. In complicated cases, of course, the expense was greater. He further stated that the patient acquired syphilis early in life, before the victim has reached an earning capacity which will enable him to cope with the situation. The result is he neglects it and loses the opportunity for cure for which, in later years, as successful merchant, banker, public official, he would give all he has.

Keidel[18] in 1931 estimated the cost to the patient of treating syphilis

in Baltimore at minimum private rates as $380 for a period of 15 months, and the cost at average rates to be $650.

Bromberg and Davis[5] believed the cost to various patients may be expected to differ because of: 1, Medical factors, particularly the state of the disease at which treatment is begun. 2, Public health provisions, particularly the extent to which health departments provide free serologic tests or arsphenamines. This is done in some localities but not in others. 3, Social and economic factors, such as the financial circumstances of patients, the prevailing scale of medical charges and of prices for drugs, at different times or in different parts of the country.

Because of these varying elements, Bromberg and Davis[5] believed no single amount can be designated as "the" cost of treating the disease. Tentative cost figures are applicable to specific local conditions and to a specified period of time. Based upon the cost of a "standard treatment" for one year, or by ascertaining the cost of treating some actual cases, these authors decided the cost to the patient of the "standard treatment" by a general practitioner, at minimum rates, for a patient not regarded as an object of charity, would be $268 for one year. The expense at the minimum rate of the specialist would be $485. The cost to the patient at the rate of the better known specialist would be $1050. If the patient were treated at a pay clinic, the cost would be, depending on the clinic, about $133, or $169 for a grade of service for which $300 to $900 more would have to be paid for private care.

For the actual treatment given to 7 patients by private practitioners, $273 to $723 was spent, with the expense for 1 individual case reaching a maximum of $1425. Bromberg and Davis[5] felt that a figure of $300 could be used as the minimum at private rates for the adequate treatment of syphilis for one year.

Moore[25a] believes that according to estimates, adequate treatment for early syphilis may be furnished at minimum clinic standards at a cost of $25 per patient; and on the basis of the highest standard of clinic practice, for $50 per patient. Gehrmann[12a] (1938) also found, after 4 years of operation of a syphilis protective program in the E. I. duPont de Nemours Company, that a complete course of treatment cost the company $50. Davis[9] estimated (in 1932) that about 80% of the population could not pay for adequate care of syphilis at private rates; about 50% of the population could pay for the adequate care of syphilis at pay clinic rates, although not at private rates; except when the usual minimum fee is cut by the physician to about half; fully one-third of the population, if infected, must receive treatment for syphilis free or for nominal amounts; and the cost of treatment is an important cause of the insufficient or inadequate therapy which many infected persons receive. In this connection Gehrmann[12b] found that "most physicians demand prices for treatment that are beyond the means of the individuals and out of reasonable proportion to their incomes."

Nelson,[29c] in discussing the provision of treatment for genito-infectious diseases in the indigent in Massachusetts, found, after 7 months of experience, that the average cost per clinic visit is approximately $1. Patients pay about 21% of this cost, and the Commonwealth pays the balance, or about $200,000 annually. For 79 cents per visit, the

Commonwealth provides not only for the treatment of these clinic patients, but also for reasonably adequate case control and case finding, done by the clinic personnel. Furthermore, the Department approves of the payment of the clinic medical personnel wherever possible, so that for slightly over 75 cents per visit, the Commonwealth purchases full treatment, follow-up, and epidemiologic service for those who are unable to pay for private medical care, and who are able to reach clinics. In order to reach individuals at distances, inaccessible from clinics, the Commonwealth has experimented with providing treatment in private practice. On proper application, the physician is allowed by the Commonwealth $2 per visit. This fee is over and above any drugs which are supplied free by the Commonwealth to physicians and clinics alike, for the treatment of syphilis. This and similar attempts to compensate private physicians on a fee basis have resulted in such abuse that efforts along these lines have been largely abandoned. No satisfactory substitute applicable to all rural areas has yet been devised, though in some sections the traveling clinic or employment of selected physicians on a salary basis to treat patients in their offices free or at a reduced fee basis has proved more practical than remuneration on a purely basis for treatment-patient visits.

If the 250,000 visits made to clinics were to be paid for at private rates, it would have cost the Commonwealth of Massachusetts $500,000 annually, instead of $200,000, and this, more than double cost, would have paid for treatment only. Actually, it has cost the Commonwealth approximately $20,000 per year to provide treatment at private rates for the relatively few patients who cannot attend the clinics. It costs another $30,000 annually to provide hospital care for patients who need and cannot pay for it.

Nelson's[29c] estimate of about $1 for the treatment of syphilis in the various Massachusetts clinics comes close to Keidel's[18] figure of $1.03 per visit for patients coming to the Johns Hopkins Hospital Clinic in 1931. Goldberg[14b] also found that $1 per clinic visit was a suitable standard figure for clinic visit costs in New York City.

Hospital, Clinic, and Laboratory Costs of Syphilis (Direct Costs). Three methods, according to Brumfield[6] have been followed as a means of obtaining data on the true costs of syphilis. In the first, used by Loeffler[20] in a survey in St. Louis in 1932, an effort was made to determine by questionnaire not only cost of treatment in private practice, but also indirect costs such as relief to families of wage earners incapacitated because of the disease and of legal proceedings involved in the supervision of prostitution. This study did not separate the costs of gonorrhea and syphilis. Brumfield and Goldberg criticized this survey on the grounds that the sample of information obtained from physicians answering the questionnaire cannot be translated to indicate the experience of those who did not reply. They contended that it is impossible to determine the proportion of hospital overhead expense which was allocated to venereal disease patients and the data obtained from agencies concerning indirect costs cannot be relied upon, since the proportion of those costs attributable to the venereal diseases is not definite. Goldberg believed that $1,000,000 of the total estimated minimum of some $2,000,000 was open to criticism.

A more reliable study of the direct costs of syphilis was made by

Thompson, Brumfield, and Caldwell.[40] They selected Baltimore in the year 1933 for their study. Their investigation was limited to those items for which they believed reasonably accurate information could be obtained. Data were secured from the actual records of the hospitals and institutions studied, and the survey was restricted to current expenditures, with no effort to estimate fixed overhead or fixed charges on capital investment, so that it included only the costs of hospitalization and clinic facilities, including laboratory services in connection with them and antisyphilitic drugs. These investigators found that the total measurable direct expense of syphilis to the city of Baltimore during 1933 was about $170,000 less about $11,000, the amount paid by patients. It is important to call attention to the fact that the total figure is the unquestioned minimum cost, and does not include any of the following indirect costs, the proportionate total of which ascribable to syphilis can only be surmised: 1, Fixed overhead of hospitals, clinics or laboratories; 2, fixed charges in capital investment of hospitals; 3, library service for blind syphilitics; 4, special schools for handicapped children; 5, blind pensions; 6, sums expended by private physicians and private laboratories; 7, fees paid by patients to private physicians and laboratories; 8, relief paid by Federal Government or local charitable, agencies to patients disabled from syphilis, or to their families; 9, legal and police measures for the repression of prostitution; 10, money wasted by patients with quack physicians and cultists; 11, cost of self-treatment at drug stores; 12, economic losses to industry and society.

Thompson and his co-workers then concluded that: 1, The total *direct* cost of syphilis to the city of Baltimore during 1933 was (roughly) $170,000; 2, indirect costs were not estimated; 3, in direct community costs alone, each new syphilitic patient was responsible for the charitable expenditure of about $18 per year; 4, only by a reduction in the incidence of syphilis can the total expenditure be decreased; 5, only by the provision of adequate ambulatory clinics can the incidence of syphilis be reduced.

Goldberg[14b] used a third method of approach in the determination of the direct cost of syphilis and gonorrhea in New York City. This survey was limited to those items included in the Baltimore study, the two diseases being considered separately. Goldberg[14b] analyzed a large number of records of representative hospitals and clinics and estimated the total cost from these. His results were surprisingly similar to those obtained in the city of Baltimore.

Brumfield (1938)[6] compared the results of a survey of the hospital, laboratory, and clinic costs of syphilis in Buffalo, New York (population approximately 573,0 '0) for 1936 with similar costs found in the Baltimore, Md. (population approximately 805,000), study by Thompson, Brumfield, and Caldwell in 1933. The total costs in each of these studies approximated each other (about $165,000 in Buffalo; about $179,000 in Baltimore), but the distribution of some of the expenditures varied considerably.

In either city the major cost was borne by public expense, by taxpayers direct, or by privately endowed charitable organizations. The cost of hospitalization of late syphilitics greatly exceeded the cost of clinic and laboratory services. This represents a great economic loss since only a few of the patients so hospitalized could be rehabilitated.

"The cost of treatment of late syphilitics in Buffalo was considerably more than in the city of Baltimore. The difference is believed to be due largely to the greater ease with which patients could obtain hospitalization in Buffalo rather than a greater prevalence of syphilis in that city. The excess cost was represented largely in the greater number of Buffalo residents cared for in New York State hospitals for mental diseases.

"A great saving in public funds could be accomplished in either city through case-finding procedures directed toward the placing of patients under treatment in the early stages of the disease and thus preventing late manifestations. The expenditure of funds for such procedures would undoubtedly be saved many times over."

Moore stated that the cost of hospitalization and of direct relief paid to disabled syphilitics, chiefly the insane, paretic, and the irremedial cardiac, may be conservatively estimated in the country as a whole as somewhere between $35,000,000 and $50,000,000 per year. This sum could largely be saved by proper attention to early syphilis.

Based upon a $25 to $50 per patient standard of treatment for clinic practice, Moore[25a] estimated the total cost of treating the known 518,000 annual fresh infections so well that incapacitation caused by late syphilis and the expense it causes could be decreased to insignificant proportions, would therefore be between $12,000,000 and $25,000,000 per year. He believed that if the more probable figures 1,000,000 patients with fresh infections should be treated each year, an annual cost of between $25,000,000 and $50,000,000 would be required. Twenty-five million dollars spent for early syphilis will do more good than a much larger amount spent for late syphilis.

Estimates have been made for various items in the cost of the care for syphilitics. Several of these are: 1, Cost of laboratory procedures for the diagnosis of syphilis; 2, cost of antisyphilitic drugs; 3, cost of epidemiologic control; 4, hospital costs.

1. Keidel[18] found that the actual cost of doing a quantitatively titered Wassermann with an additional flocculation procedure on each sample of blood submitted in a small but reliable laboratory, doing 200 tests per month, was $1.63 per specimen. If 500 tests per month were run, the estimated cost would be 66 cents. The serologic laboratory at the Johns Hopkins Hospital, doing over 50,000 tests per year, does them at an average total cost of 29 cents each. The Massachusetts Department of Health (Nelson and Crain[30]) doing 200,000 tests annually, can do the serologic tests at 12 cents each. Webb and Sellers[47] found that 46 state and 15 city laboratories performed 2,854,000 tests in 1935. Based on Keidel's lowest cost, this comes to $828,000 annually. Brumfield,[6] in his comparison of Baltimore and Buffalo costs, noted a per capita expense of $0.043 for Baltimore and $0.044 for Buffalo. His study, however, failed to mention the actual cost per test. Gehrmann[12b] (1938) stated the cost to the du Pont de Nemours Company for a Kahn test was 20 cents.

2. *The cost of antisyphilitic drugs* is variable, dependent upon the types of drugs, the locality in which the drugs are purchased, and the arrangements with manufacturers, which the various agencies supplying the drugs make. The cost of antisyphilitic drugs in Baltimore was about $7000 while only about $2000 were spent in Buffalo. The costs

of antisyphilitic drugs in Baltimore were estimated while in Buffalo figures were supplied by the New York State Department of Health.[40]

3. Ingraham[17] has estimated the cost of epidemiologic control work in clinic practice. The cost for complete service includes expenditures directed toward: 1, Instructing the patient. 2, Obtaining usable information concerning sources of infection and contacts, and bringing these contacts under observation. 3, Correspondence, telephone calls, and home visits involved in keeping the patient coming in regularly for treatment.

These figures are on a yearly basis. The total cost of uncovering 0.36 infected contacts per each newly infected case, and of keeping some 35 per cent of patients under active therapy for a year in Clinic II in New Jersey, amounted to $11.36 per patient per year. This cost in Clinic I in New Jersey, which presents a relatively lower contact rate (0.23 per infected patient) but a higher case-holding ability (57% success) amounts to $16.58 per patient per year. In the University of Pennsylvania Syphilis Clinic, the cost was $5.99 for successful follow-up service, and for successful contact tracing, it is $5.22 per patient. The total cost per patient is $11.21. This is about equal to the figure for Clinic II in New Jersey.

4. The cost for the hospitalization of syphilitics has also been estimated. This cost for late syphilis is more than the costs of clinic and laboratory services. In Buffalo[6] this item represented about two-thirds of the total expenditures. In Baltimore it was less than half of the total outlay. Goldberg[14b] found that the New York City hospitals and the State hospitals admitting patients from the city were obliged to expend more than $1,000,000.

Estimated Cost of Maintaining a Program for the Control of Gonorrhea and Syphilis. The Advisory Committee to the United States Public Health Service[1] in 1935 prescribed a program for the control of gonorrhea and syphilis by state and local health departments. The cost of carrying out these recommendations has been estimated for Massachusetts by Nelson.[29a] It would require a budget about twice as large as the budget in force in 1935 for the essential program and one about four times as large for the recommended program.

Nelson[29a] believed that if total appropriations from all public funds for the control of communicable diseases are taken into consideration, that part spent for the control of gonorrhea and syphilis must be relatively insignificant. On that basis, the expenditure by the state of between $300,000 and $400,000 annually cannot be considered as a disproportionately large sum for the control of two such prevalent and economically serious diseases as syphilis and gonorrhea. He further stated "that large sums of money have been appropriated for the control of tuberculosis, for the purification and protection of water supply, and for the control of cancer because the public has learned that these things are worth spending money for. The need should determine the expenditure rather than relative prevalence. Nothing could be more striking than the $1,272,580 spent by the State for the control of tuberculosis (in 1935) compared with $259,425 spent for the control of other communicable diseases, whereas the reported prevalence of tuberculosis is only 5.1% of the reported prevalence of all communicable

diseases. On the basis of relative prevalence, only $13,000 should be spent on tuberculosis."

The Massachusetts Department of Public Health spends 6.2 cents per capita exclusive of Social Security funds on syphilis. If the same per capita rate were expended by all of the State Departments of Health, the total outlay would only be about $8,000,000 in this country of an estimated 130,000,000 population. This sum is small in comparison with the $50,000,000 needed for the adequate care at clinic rates of only those fresh infections which come to medical attention annually.

It may be pertinent to comment here briefly on the question of the reaction of many physicians to the state and national program, based upon fears of socialization of medicine. While it is definitely not appropriate to make polemic issue of this problem here, the analysis by Gilman[13] of the competition of the State with private practice reduces the arguments to absurdity. For example, he calculated, on the basis of $3,000,000, appropriation for the whole of the United States set aside for syphilis control for 1938 that a sum of 80 cents per year per clinic patient was available. This figure is based on the assumption that all of the money is expended in syphilis control.

Costs, Direct and Indirect, for Various Aspects of the Syphilis Problem. *Cost of Syphilis to Industry and Labor.* In the review of Syphilis in Industry by Stokes, Beerman, and Ingraham[39] it was pointed out that figures for the cure of syphilis in industry have still a somewhat speculative character. Many of them are old and possibly outdated; based on individual surveys of industries whose identities are concealed and whose representative character for the problem in general or the country at large cannot be determined. Among the most quoted estimates are those of Parker[31] (1932), including 12% syphilis in a group of railway employees exhibiting delayed convalescence and disability whose total loss of time represented 13,946 days, and $48,711. A large industrial concern, unnamed, whose personnel efficiency had dropped below expectations, found that 1 in 10 employees had gonorrhea or syphilis, 68% of the non-effective employees were on the sick list because of these diseases, and those venereally diseased had lost three times as much time as persons not affected. Each person with syphilis or gonorrhea was paying out an average of $75 a year for such treatment as was being given. The establishment of a clinic within the industry for adequate treatment and assistance to these persons presently offset the cost to the establishment by increased production. A West Virginia manufacturing concern, as a result of the installation of a clinic for venereal disease costing $5000 to $6000 for the first year, sustained an increased efficiency of 35%.

"It is clear from a review of the literature that statistics providing adequate differentiation among types of employees, types of industry, and obtained by methods other than mere routine serologic testing of blood, are really needed before the problem can be envisaged in its entirety, and principles formulated."

Among the general male population, aged 15 to 45, the number of days lost from work through venereal diseases is at least equal to 21,000,000 per year. At the average wage of $4 per day, $84,000,000

in wages are lost, to say nothing of the cost to employers, compensation, medical costs, and labor turnover.[2]

Moore[25b] has made a thorough discussion of the problems, social and economic, involved in syphilis and unemployment. He has not, however, estimated the possible financial cost of this important subject.

Syphilis and Crime. Without entering into a discussion of the social implications involved in the problem of syphilis and crime, it is interesting, even if not more than coincidental, that among prisoners the incidence of syphilis is higher than in non-criminal groups. This whole subject was discussed by Church[7] in 1938.

Parran's Committee[15,16,19,22,28,36,37,41–43] reported from the literature, among 119,000 individuals which represents the average prison population for Federal and State prisons in the United States, there were on an average of from 160 to 170 per 1000 individuals with positive blood tests for syphilis.

Surgeon Hawk[15] of the United States Public Health Service found in the prisoners of the penitentiary at Fort Leavenworth, that the prevalence was highest among negroes, 36.4%; 34.9% for the red-brown races; 19.1% for the Caucasian race; and 11.4% for the Mongolian race, with a general average prevalence of 21.7% for a period of $2\frac{1}{2}$ years. Keil[19] found 18.2% positive blood tests in an Ohio penitentiary. Heller[16] (1936) in a study of the short-term prisoners in a penitentiary, in eastern Tennessee, found positive blood tests for syphilis in 20.2% of the whites and 44.6% of the negroes with an average percentage of 29.3%. As a control for the incidence among these two groups, Heller used statistics on negro families in rural Tennessee, among whom 26% had positive blood tests, while a white survey in an industrial plant in the same section of the State yielded 4.1% positive tests. Negro males in an industrial project yielded 15% positive tests. Heller also found that 30.2% positive serologic tests in the spinal fluid in the whites; 21.1% in the negroes, and an average of 24.6% in both. He felt that the actual percentage may be higher since only patients with positive blood tests had their spinal fluids examined. Of those with neurosyphilis, 45% showed enough positive signs to make the diagnosis clinically. Church[7] also cited a number of statistics regarding the association of syphilis and homicide.

It is obvious, although syphilis is not blamed for criminality, from the frequence of syphilis among criminals that this disease cost the community a considerable amount of money. The exact sum is by no means calculable.

Syphilis and Insurance. The problem of insurance and syphilis is receiving increasing attention. There are no accurate statistics on the number of individuals who sustain insurance benefits or economic losses in the form of increased premiums because of syphilis. Compensation paid because of the contributory effects of syphilis is likewise an indefinite quantity. The detection of syphilis in applicants for insurance can be facilitated by the use of a sensitive precipitation test as suggested by Rein, LeMoine, and Stephens.[33] Murrell and Manson[27] and Short and Kelley[35] in recent papers made observations on the incidence of syphilis among insurance applicants and suggestions for the equitable solution of this problem.

Cost of Quack Medicine and Self-prescribing. This phase of the cost of syphilis is again one which defies estimation. It is, however, recognized that it represents a large figure and in the careful study of Edwards and Kinsie[11] there is some indication "that the sale of such patent remedies is now even greater in volume than 6 to 8 years ago." They further found that large numbers of charlatans, herbalists, and other unlicensed practitioners are treating many persons having syphilis and gonorrhea.

Syphilis and Death. This item of cost of syphilis is difficult to estimate. Not only are the deaths directly attributed to syphilis not reported by physicians, but many are actually unrecognized. In addition, the cost of premature deaths is an item which must be taken into account. Usilton[44b] determined that life expectancy of males with syphilis is shortened from that in the general population from 30 to 60 by 17% in the white males and 30% in the negro males. The preliminary Mortality Summary for Large Cities (1939)[26] showed a rate of deaths from syphilis of 9.8 (1936) per 100,000 population; 10.2 per 100,000 population in 1937; and 9.7 per 100,000 population in 1938.

On the basis of extensive literature Parran and his Committee[32] from the United States Public Health Service estimated that approximately 40,000 deaths from cardiovascular syphilis occur every year in the United States, at least 6.5% of which are syphilitic in origin. Since each death represents a loss of from 19 to 23 years of life, it is estimated the total loss of life from cardiovascular syphilis is around 800,000 to 850,000 years annually. Deaths from paresis represent a loss of about 100,000 years annually.

Cost and Loss From Syphilis Blindness. This subject has been admirably summarized by Surgeon C. E. Rice[34] of the United States Public Health Service. After a preliminary survey of the various factors involved in the incidence and cost of this phase of syphilis, Rice[34] found that syphilitic blindness costs the United States about $10,000,000 in the loss of earnings and in costs of supporting these blind individuals.

Syphilis accounts for about an average of 15% of the blindness. Rice has cited estimates ranging close to this average figure, which he used as the basis for his calculations. While this average percentage is generally acceptable, it is worth noting that recent authorization studies based on fairly large series of cases have given relatively lower figures (Berens, Kerby, and McKay,[4] 5.3%; Berens and Goldberg,[3] 6%; Cowan and Sinclair,[8] 9.4% among applicants for pensions for the blind in Pennsylvania; Long and Goldberg[21] cite: 0.45% interstitial keratitis in eye cases in Boston; National Society for the Prevention of Blindness, 15% of the blindness due to syphilis among about 5000 applications for pensions for the blind, University of California Dispensary, 9.5%). Even if 15% is considered a little high as the average incidence of syphilitic blindness, Rice's[34] figures are so conservative that the minimum cost of about $10,000,000 is unquestionable.

The statistics, roughly estimated, for the State of Pennsylvania, have been given to me in a personal communication by Miss E. M. Carpenter, of the Philadelphia Committee for the Prevention of Blindness, Inc. Eighteen per cent of a total of 27,000 applicants for blind pensions have syphilis (13,000 were granted pensions). The average cost

per year per person as a pensioner is $360. It is estimated that it costs $10,500 to educate one blind child through twelve grades. There are about 500 children in two schools for the blind in Pennsylvania. One-third of these children are presumed to be syphilitic. The cost for this education is supplied by the State (75%) and local philanthropies (25%).

Costs of Cardiovascular Syphilis. Ten to 18 per cent of the load of cardiovascular clinics has been estimated as due to syphilis. It is obvious that a specific estimate of the total cost, both direct and indirect, of this large amount of disability due to syphilis can hardly be accurately estimated. However, certain parts of the costs can be approximated. For example, Brumfield[6] showed that the hospital costs in Baltimore for cardiovascular syphilis was about $11,000 whereas for Buffalo the cost for hospitalization was about $8000. It is pertinent to realize that the expenditure for hospital care for cardiovascular syphilis is apparently a lighter burden than that for neurosyphilis, but this must not be interpreted to indicate that cardiovascular syphilis is relatively unimportant, since it results in death relatively soon, or the patient may be rehabilitated to the extent that he can be cared for at home, even though he might be unable to return to gainful employment. The result is that the economic losses from this manifestation will be represented largely in indirect costs.

Neurosyphilis. The incidence of neurosyphilis is one of the major factors in mental disease. Merriman[24] (1935) estimated that neurosyphilis occasioned 11.3% of all admissions to civil state hospitals during the year ending 1933, and he restated the estimate that neurosyphilis cost the State of New York alone $13,500,000 during the year 1931. Malcolm H. Merrill,[23] Chief of the Bureau of Venereal Diseases of the State of California, estimated that this State is forced to spend approximately $250,000 a year for the care of the syphilitic insane who are only one small group of those who are dependent because their syphilis was undiscovered or untreated. An editorial, commenting on "Dangerous People At Large,"[10] pointed out that the hospital facilities used "by our paretic company will represent an investment of over $1,250,000." Brumfield[6] found the hospital costs for neurosyphilis in Baltimore and Buffalo to be the greatest expense in either city. In Baltimore, this item cost about $51,000, whereas in Buffalo the cost of hospitalization was about $95,000.

In addition to the economic losses and the cost for hospitalization, as well as other indirect costs of neurosyphilis, paresis and tabes are a factor in the death rate from syphilis. Fortunately, this cost appears to be decreasing.[33]

As was stated in the beginning of this survey, one cannot estimate with any degree of exactness the actual cost of syphilis. The reliability of the data given is questionable, regardless of how carefully they were compiled. One thing is certain. The cost of syphilis is enormous, even in these days when millions or billions of dollars are spent by governments daily. Treatment for syphilis will wholly prevent this unnecessary expense. It is obvious that untreated syphilis is a luxury for any individual or community.

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REFERENCES.

(1.) Advisory Committee to the United States Public Health Service, **R. A. Vonderlehr** et al., Ven. Dis. Inform., **17**, 1, 1936. (2.) Am. Soc. Hyg. Assn., Hidden Costs in Industry, Pub. 751, 1931. (3.) **Berens, C.**, and **Goldberg, J. A.**: J. Am. Med. Assn., **109**, 777, 1937. (4.) **Berens, C., Kerby, C. E.**, and **McKay, E. C.**: Ibid., **105**, 1949, 1935. (5.) **Bromberg, L.**, and **Davis, M. M.**: J. Soc. Hyg., **18**, 365, 1932. (6.) **Brumfield, W. A., Jr.**: Ven. Dis. Inform., **20**, 63, 1939. (7.) **Church, F. H.**: Med. Rec., **147**, 49, 1938. (8.) **Cowan, A.**, and **Sinclair, S. M.**: Trans. Sec. Ophth. Am. Med. Assn., p. 74, 1936. (9.) **Davis, M. M.**: J. Soc. Hyg., **18**, 378, 1932. (10.) Editorial: New York State J. Med., **34**, 613, 1934. (11.) **Edwards, M. S.**, and **Kinsie, P. M.**: Ven. Dis. Inform., **21**, 1, 1940. (12.) **Gehrmann, G. H.**: (*a*) Ven. Dis. Inform., **17**, 227, 1936; (*b*) Am. J. Syph., Gon., and Ven. Dis., **22**, 623, 1938. (13.) **Gilman, R. L.**: Penna. Med. J., **42**, 241, 1938. (14.) **Goldberg, J. A.**: (*a*) Soc. Hyg. Com., New York Tuberc. and Health Assn., New York, 1936; (*b*) Ven. Dis. Inform., **19**, 287, 1938. (15.) **Hawk, F. A.**: Ven. Dis. Inform., **15**, 267, 1934. (16.) **Heller, J. R.**: Ibid., **17**, 65, 1936. (17.) **Ingraham, N. R., Jr.**: Ven. Dis. Inform., **19**, 61, 1938. (18.) **Keidel, A.**: Arch. Derm. and Syph., **25**, 470, 1932. (19.) **Keil, G. W.**: J. Am. Med. Assn., **94**, 2084, 1930. (20.) **Loeffler, H. C.**: Cost of Venereal Disease to St. Louis, St. Louis, Mo., Social Hyg. Assn., Inc., 1933. (21.) **Long, W. B.**, and **Goldberg, J. A.**: Social Hygiene, Philadelphia, Lea & Febiger, 1938. (22.) **Martin, W. B.**: Arch. Neurol. and Psychiat., **18**, 1051, 1927. (23.) **Merrill, M. H.**: Report of the Bureau of Venereal Diseases, State of Calif., Feb. 1, 1937 to June 30, 1938, p. 81. (24.) **Merriman, W. E.**: J. Soc. Hyg., **21**, 164, 1935.

(25.) **Moore, J. E.**: (*a*) Ven. Dis. Inform. (Suppl. 3), p. 84, 1936. (*b*) J. Indust. Hyg., **19**, 189, 1937. (26.) Mortality Summary for Large Cities, 1939, Bureau of the Census, Dept. of Commerce, Pub. Health Rept., **55**, 211, 1940. (27.) **Murrell, T. W.**, and **Manson, R. C.**: South. Med. J., **32**, 322, 1939. (28.) **Nagel, G. W.**: Calif. State J. Med., **19**, 193, 1921. (29.) **Nelson, N. A.**: (*a*) Ven. Dis. Inform., **17**, 359, 1936; (*b*) J. Am. Med. Assn., **106**, 105, 1936; (*c*) Am. J. Syph., Gonor., and Ven. Dis., **22**, 669, 1938. (30.) **Nelson, N. A.**, and **Crain, G. L.**: Syphilis, Gonorrhea and the Public Health, New York, The Macmillan Company, 1938. (31.) **Parker, V. H.**: Hidden Problems in Hard Times, Am. Soc. Hyg. Assn., 1932. (32.) **Parran, T.**, et al.: Ven. Dis. Inform. (Suppl. 3), p. 125, 1936. (33.) **Rein, C. R., LeMoine, M.**, and **Stephens, M. G.**: J. Soc. Hyg., **23**, 258, 1937. (34.) **Rice, C. E.**: Ven. Dis. Inform., **20**, 91, 1939. (35.) **Short, J. J.**, and **Kelley, M. F.**: Proc. Life Extension Examiners, **1**, 6, 1939. (36.) **Squire, A. O.**: Med. Times, **54**, 206, 1924. (37.) **Stanley, L. L.**: J. Am. Med. Assn., **92**, 1928, 1929. (38.) **Stokes, J. H.**: Today's World Problem in Disease Prevention, U. S. Pub. Health. Serv., Washington, D. C., 1919. (39.) **Stokes, J. H., Beerman, H.**, and **Ingraham, N. R., Jr.**: Am. J. Med. Sci., **196**, 600, 1938. (40.) **Thompson, W. C., Brumfield, W. A.**, and **Caldwell, L.**: Am. J. Syph., Gon., and Ven. Dis., **20**, 243, 1936. (41.) U. S. Bureau of Prisons, Ann. Rept., Federal, Penal and Correctional Institutions, Fiscal Year 1927–1928, Fort Leavenworth, U. S. Penitentiary Press. (42.) U. S. Bureau of Census, Prisoners in the State and Federal Prisons and Reformatories, 1933, Washington, Government Printing Office. (43.) U. S. Bureau of Prisons, Federal Offenders, 1933–34, pp. 15, 77, Fort Leavenworth, Federal Prison Industries, Inc., Press. (44.) **Usilton, L. J.**: (*a*) Ven. Dis. Inform., **16**, 147, 1935; (*b*) Ibid., **18**, 231, 1937. (45.) **Vonderlehr, R. A.**: Ibid. (Suppl. 3), p. 125, 1936. (46.) **Vonderlehr, R. A.**, and **Usilton, L. J.**: Ibid., **19**, 396, 1938. (47.) **Webb, E. L.**, and **Sellers, T. F.**: Am. J. Pub. Health, **26**, 918, 1936.

PHYSIOLOGY

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Simultaneous Renal and Hepatic Excretion of Water and Various Dyes in Rabbits. William E. Ehrich (Department of Pathology, School of Medicine, University of Pennsylvania). The excretion of water,

cyanol and azofuchsin I were studied simultaneously in simple bile drainage experiments and in those in which urea was given to stimulate diuresis. In addition, experiments were performed in which either the common bile duct or the renal arteries and veins were ligated. Ligation of the common bile duct did not as a rule influence diuresis, and administration of urea did not influence the bile rate, while ligation of the renal arteries and veins was followed by a drop in the rate of bile excretion. The renal excretion of the dyes depended chiefly on the urine rate in all experiments, more dye being excreted with better diuresis and *vice versa*. The hepatic excretion of the dyes on the other hand was not merely a function of the bile rate, but depended on both the bile rate and the urine rate (*i. e.*, the renal elimination of the dyes). The faster the bile rate and the slower the renal elimination of the dyes, the greater the amount of dye that was excreted in the bile.

The Biologic Activity of Some Cortin-like Compounds. DWIGHT J. INGLE (George S. Cox Medical Research Institute, University of Pennsylvania). Desoxy-corticosterone is the most active of the known steroid compounds in its life-maintaining capacity. The compound 17-oxy-11-dehydro-corticosterone has little or no life maintenance effect. The earlier observation has been confirmed that 17-hydroxy-11-dehydro-corticosterone has an apparently greater effect upon the work performance of adrenalectomized rats than does desoxy-corticosterone when the first 24 hours following operation are used as a test period.

In addition, adrenalectomized male rats having an initial body weight of 180 gm. were treated for 1 week with these two compounds and at the end of this period their work capacity was studied. The rats treated with desoxy-corticosterone gained in weight even when the doses were small, and although their capacity to work was improved over that of untreated animals, their performance was poor even when as much as 10 mg. was administered daily. All of the animals treated with 17-hydroxy-11-dehydro-corticosterone lost weight to the same extent as untreated animals, but their work performance was improved above that of the animals treated with desoxy-corticosterone. Similar animals treated with a mixture of desoxy-corticosterone and 17-hydroxy-11-dehydro-corticosterone performed more work than animals treated with an equal quantity of the single substances.

Although the results may be due to changes in the efficiency of utilization of these compounds when they are administered in different test situations, the findings are also in harmony with the hypothesis that there are qualitative differences in the biologic effects of some of the cortin-like compounds.

The Effect of Temperature and of Starvation Upon Growth of Frog Carcinoma. BALDUIN LUCKÉ and HANS SCHLUMBERGER (Laboratory of Pathology, School of Medicine, University of Pennsylvania). For studying the effect of temperature on growth of tumors, the kidney carcinoma of the leopard frog, *Rana pipiens*, is particularly good material, as this tumor grows well when inoculated into the anterior chamber of the eye where it may be kept under continued observation (*J. Exp. Med.*, **70**, 251, 1939); and as it is able to establish itself and increase in size at temperature differences of at least 20° C.

In the first series of experiments, frogs, immediately after being inoculated, were transferred to a constant temperature room, at 7° C., control groups being kept in the vivarium at 22° C. They were observed for 2 to 6 months, and during this time they received no food, as frogs at the lower temperature will not eat. It was found that the tumors were able to establish themselves and grow at both temperatures, though the proportion of takes was slightly less at 7° than at 22°. Massive tumors, however, developed only at 22°; this fact seems to be due to more effective vascularization at the higher temperature. When the frogs with large, well-vascularized tumors were transferred from the vivarium to the cold room, growth of tumors continued, but at a slower rate.

In the second series of experiments, the effect of temperature was studied on tumors that had already become established. Following inoculation in the anterior chamber, frogs were kept in the vivarium for 2 or 3 weeks, or until the transplants showed evidence of beginning growth. The frogs were then transferred to constant temperature rooms, at 7° C. and at 28°, respectively. It was found that the rate of growth was greater at the higher temperature, though there was little difference in the size which was finally attained. Regression of the tumors developed in a higher percentage at 28° than at the lower temperature.

In a final group of experiments, the combined effects of extreme starvation and low temperature was investigated. Markedly emaciated frogs which had been kept at 7° for several months were inoculated and then returned to the cold room; as controls, well-nourished frogs with intraocular transplants were maintained at 28°. It was found that even in the starved animals, cold did not prevent growth of transplants, though growth was less vigorous than in the control group.

The general conclusion to be drawn from these experiments is that low temperature, 7° C., does not arrest nor change the mode of growth of frog carcinoma transplanted to the anterior chamber; it does, however, reduce the velocity of growth, possibly by preventing early vascularization. High temperature, 28° C., while increasing velocity of growth, also tends to lead to its earlier decline and to retrogression of the tumors.

Surgical Correction of Hypomenorrhea and Hypermenorrhea by Isoplastic Grafts. MICHAEL JOHN BENNETT (Broad Street Hospital). The ovarian isoplast is produced by an abdominal operation which interchanges a portion of one ovary from each of 2 patients. Fifty such grafts have been made in this hospital since February, 1935. The patients are carefully selected after 2 to 24 months of preliminary study in which it is established that one of each pair possesses ovaries of the hyperinterstitial, the other of the hypointerstitial, type.

At the time of operation, the hypointerstitial and hyperinterstitial ovaries are simultaneously resected at the hilus without hemostasis. The resected tissue is immediately transferred from one hilus to the other. The peritoneal coat of the stump and the peritoneal coat of the transported ovary are coapted by means of a continuous suture of No. 00 chromic catgut on an atraumatic needle. No complications have followed.

Following these operations an improvement in ovarian rhythm, appearance of vaginal smears, esterone and prolan concentrations, and chemical constituents of the blood have been noted and no patient has required a continuation of hormonal medication. We believe that ovarian isoplasty tends to stabilize metabolic imbalance caused by ovarian dysfunction and that such grafts will grow with a normal nerve and blood supply if they are made in the manner described and in carefully selected patients.

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